Modelling healthcare provision for an infectious disease using optimal control

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Award date:
2010

Awarding institution:
University of Bath

Modelling Healthcare Provision for an Infectious Disease using Optimal Control

submitted by

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for the degree of Doctor of Philosophy

of the

University of Bath

Department of Mathematical Sciences

February 2010

Acknowledgments

I've really enjoyed my time at the University of Bath and thanks must go to my supervisor, Jane White, for all her help and encouragement over the last three and a half years and EPSRC for funding me. Thanks also to everyone in the Department of Mathematical Sciences and the Centre for Mathematical Biology for making it possible to complete this Ph.D.; I would like to thank Matt, Damien, Barry and Jason, who all made the introduction to a Ph.D. much easier! I would especially like to thank Zoë for everything over the last three and a half years - teaching me to knit, the many discussions of our work and the hot chocolate breaks. Just remember, there is no spoon!

I would like to thank my family - Sheila, Rob, Simon and Jen - for helping me to reach this point. Their support and love has made this work possible.

Finally, I would like to thank my fiancé James. His willingness to sit for hours whilst I practiced presentations and to discuss my work whenever necessary has been amazing. For supporting me throughout this process, and for whisking me away on holiday to balance the demands of work, I am very grateful. We have made this journey together - thank you.

Summary

The development of a vaccine against some strains of the human papillomavirus (HPV) has led to many interesting public health questions [1]. We address some of these questions in the following work. We develop a compartmental mathematical model and examine the effect of waning immunity, vaccinating individuals prior to their becoming sexually active and the current government policy of vaccinating only females [2]. We calculate parameters based on data. We consider both time-dependent and age-dependent ODE models and an age- and time-dependent PDE model and compare the results. We find the "effective" R_0 value, R_0^ϵ, for the time-dependent models. We introduce optimal control to both the time-dependent and age-dependent ODE models to assess the most cost-effective method for introducing the vaccine into a population.

We find that the duration of protection offered by the vaccine can influence whether it is possible to eradicate infection from the population. We find the critical proportion to vaccinate to eradicate the disease. We see that introducing male vaccination would lead to a greater proportion of individuals to be vaccinated if the disease is to be eradicated. The PDE model shows that the proportion of females vaccinated has a large impact on the proportion of females infected. We show that it is cost-effective to vaccinate males and females. Our results support current government policy for age of vaccination [2].

We conclude that potential waning immunity will impact the success of the vaccine. We broadly support government policy for vaccination but recommend including male vaccination to most cost-effectively eradicate the disease.

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Chapter 1

Introduction and Literature Review

The aim of this thesis is to consider the effect that the implementation of a new health-care policy has on the spread of an infectious disease in a population. More specifically, we consider the introduction of a vaccination programme, targeted at a specific group of individuals, for a sexually transmitted disease. We consider the implications of vaccinating individuals before they become sexually active and the possibility of waning immunity from the vaccination. We model this mathematically, using compartmental, population-level models, represented by systems of differential equations. We also assess the cost-effectiveness of the vaccination strategy using optimal control.

This research is motivated by the introduction of a national vaccination programme against certain sexually transmitted strains of the human papillomavirus (HPV). This vaccine is not the first against a sexually transmitted disease - vaccines exist both for hepatitis B and herpes simplex type-2 (HSV-2) [9] - but neither of these are routinely offered in the UK for adolescents [4]. In the UK, vaccination against HPV strains -16 and -18 is targeted at 12-13 year old females, with a 'catch-up' vaccination programme being offered up to the age of 18 [5]. This vaccination policy means that the majority of females are vaccinated before they become sexually active. Two questions naturally arise; What happens if immunity provided by the vaccine wanes? If it does, how will the interaction between waning immunity and many individuals being non-sexually active when vaccinated impact on the potential success of vaccination? These questions are addressed in the following work.

The second part of the research presented is concerned with the cost-effectiveness of the vaccine. Unlike previous studies for the HPV vaccine, we consider this issue by using optimal control to determine the most cost-effective method for vaccinating

individuals. We also consider whether male vaccination can be cost-effective, as current policy is to only vaccinate females [2]. This research gives an interesting counterpoint to the economic cost-effectiveness analyses that have so far been carried out [10, 11, 12].

1.1 Human Papillomavirus: Biological and Background Information

A virus that is a causal factor in the development of cervical cancer, sexually transmitted strains of the human papillomavirus (HPV) are thought to affect about 80% of the sexually active female population at some point during their lives [13]. Of these, about 10-20% have a persistent infection (the definition of this differs greatly in the literature, but most sources put it as somewhere between 6 months and 2 or more years), say an infection lasting 2 or more years [14]. The likelihood of developing pre-cancerous lesions increases with long-term infection; for type HPV-16, there is a 40% chance of cervical intraepithelial neoplasia (CIN) after infection lasting 5 or more years [15].

Of over 120 different strains of HPV which have been identified, only about 40 are thought to infect the anogenital area, of which two strains, -6 and -11, cause 90% of genital warts [16]. Further to that, only 13-18 of these strains are thought to be carcinogenic [17]. The connection between HPV and cervical cancer has been suspected since the 1970s, a discovery that was aided by the knowledge that papillomaviruses cause cancer in animals [18]. Studies showed that HPV could be found in 99.7% of cervical cancer tumours, leading the International Agency for Research on Cancer (IARC) in 1995 to classify types HPV-16 and HPV-18 as carcinogenic [19]. Further studies led to HPV types -31, -33, -35, -45 also being classified as carcinogenic [20], but it is types -16 and -18 that are considered to be the most prevalent of the carcinogenic types throughout the world, causing about 70% of all cervical cancer [17]. Since HPV has been identified as a factor in cervical cancer (and now in some other genital and anal cancers as well [17]), investigations have been under way to try and find a way of preventing it. This is important because worldwide, cervical cancer is the second most common form of cancer, with 493,000 deaths attributed to it in 2002. At present, 80% of deaths occur in developing countries, with the proportion expected to rise to 90% by the year 2020 [21]. It is one of the biggest causes of number of years of life lost [14].

Current processes for prevention and cure of cervical cancer and HPV rely mainly on screening. In the UK, Pap smears are used to test for abnormalities in the cells at the cervix, as this could be an indication of pre-cancerous lesions. Women are advised to be tested at regular intervals, the intervals differing depending on age [6]. This has been a successful policy - since the introduction of Pap smears 50 years ago, cases

of cervical cancer have been reduced by approximately 50% [14]. However, there are flaws in the system. Screening does not always reveal the presence of HPV-DNA, and while there are tests that will do this more effectively, they are then less effective at identifying pre-cancerous cells [22]. Also, not all women will be screened; the rate of screening seems to be falling in the population as a whole, and some sectors of the community traditionally have a poor uptake rate [15].

Two prophylactic vaccines have been developed that protect against some strains of HPV, with a view to dramatically reducing the cases of cervical cancer. The vaccines have been produced by Merck and GlaxoSmithKline; the Merck vaccine protects against strains -6, -11, -16, -18, and the GlaxoSmithKline vaccine protects against strains -16 and -18 [15]. These vaccines are widely welcomed, as in testing they have shown close to 100% efficacy against these strains of HPV [23]. As they are so new, it is not clear how long they are expected to remain effective. Current trials show that they are still effective after 5 years, but the true duration of protection will only become evident in the next 10-20 years [18]. By preventing strains -16 and -18, these vaccines could play a major part in reducing cervical cancer, but there are other factors to be considered. Firstly, the cost of the vaccine is very high, and will almost certainly be prohibitive for some countries; for the UK, vaccine cost has been estimated (without administration costs) at approximately £60 per dose [10]. Secondly, the vaccine is a course of three injections at 0, 2 and 6 months so there is a question about uptake. If an individual does not complete the course, they will need to start the course from the beginning again to be protected, which would be costly. However, the cost of screening and treatment (if necessary) is also expensive, as is the treatment of genital warts. From a cost-effectiveness viewpoint, questions also need to be raised about who should receive the vaccine (Dushyant Mital, personal communication).

As evidence begins to emerge about a connection between HPV and other genital cancers [17], it may indicate that males should also be vaccinated. Another consideration is whether the vaccine could have a negative effect on the cervical cancer rates; as HPV strains -16 and -18 only cause about 70% of all cervical cancer, there is some concern that other carcinogenic strains will take their place. Also, some studies have suggested that strains -6 and -11 can offer some protection against other, more carcinogenic strains, so reducing the rates of these may not be beneficial [24]. Studies into whether an HPV-16/18 vaccine provides cross-protection against other strains have been conducted, and some suggest that there is a high level of cross-protection against HPV-31 and -45. The protection against -45 seems much higher, with 94% of vaccinated women also being protected against it, whereas 54% of vaccinated women were protected against -31 [15]. Another concern is that women will assume they are fully

protected once they have been vaccinated and so no longer need smears, although it will still be crucial that women are screened [24]. Hildesheim *et al.* (2006) [1] gave the issues still to be addressed, which included duration of protection, the optimal age for vaccination, and how to implement the vaccine. These ideas provide a starting point for developing a model to address some of the pertinent questions surrounding the HPV vaccine.

Prior to building a model, it is important to understand how the human papillomavirus works, and also how the vaccine works. One of the difficulties facing researchers is that very little is known about this virus. It is not clear for example whether the virus ever leaves the system once infected, or whether it enters a latent period [25]. It is also not clear why some people and not others have a persistent infection, although it is suspected this is due in part to the strain of the virus and in part to the host's susceptibility to the disease [25]. Another problem is that if a woman presents with an HPV infection at two or three consecutive screening sessions, it is very difficult to know whether it is the same infection each time or a different infection [25]. However, as not all women with persistent HPV infections go on to develop cancer, questions also remain as to why some women are susceptible when others are not. There are some opinions on this; other risk factors such as smoking and the number of full-term pregnancies are thought to play a part [19]. Also, is it not clear whether an individual can develop natural immunity to the virus once infected [17]. The immune response to HPV is not completely understood; it has been noticed that in some women with skin warts there was a serum Immunoglobulin G (IgG) response (this is a response that occurs towards the end of a first, or primary, immune response) to the virus. This response only seems to occur in women who have had a previous infection, implying that some memory of the virus remains in the body [20]. Man (1998) [26] suggests that natural infection does not induce a strong antibody response and that the vaccine will need to induce a strong response for prophylaxis to occur, and a study done in Costa Rica found no evidence of protective immunity, and suggested that the immune response from natural infection may not be strong enough to provide immunity [27].

Other issues arise, for example the majority of HPV infections are asymptomatic, so people do not seek treatment, and therefore the true scale of the disease may never be known. The strains that can display symptoms - namely, strains such as -6 and -11 that cause genital warts - are not considered to be carcinogenic, so it is the more dangerous strains that may be undetected. However, even if detected, much uncertainty remains. For example, will the patient go on to develop cervical cancer? How long will it take for pre-cancerous lesions (which may or may not lead to cancer) to manifest? This has been measured at anything from a few months to several years [17]. If lesions do develop,

what is the likelihood that they will progress to the more serious pre-cancerous stages, or indeed, to cancer itself? These are currently all unknown quantities, and need to be taken into account when developing a model. Studies have been undertaken to try and determine more accurately the answers to these questions, but the results tend to vary wildly, leaving us without a clear picture.

It is not yet fully understood what causes an HPV infection to progress to cervical cancer. The length of time it takes for any lesions that develop to progress to cancer, if indeed they do at all, is very variable; they can take anything from a few months to several years. It is also thought the Human Leukocyte Antigens may play a part in a person's susceptibility to cancer. There are risk factors involved; a person's age and sexual history (number of lifetime partners, recent partners) are considered strong indicators of the likelihood of contracting cervical cancer [17]. Other factors that could increase the risk of developing cervical cancer are viral load, other sexually transmitted infections (STIs), circumcision (may help reduce transmissibility), and condom use. However, the evidence is not always particularly strong, and at times is contradictory. Issues that still need to be explored are the natural history of the virus, and the viral load pattern [28]. It is also not clear what can cause an HPV infection to become persistent, or lead to cervical cancer, other than the HPV type and its variant. It is thought that the host's immune system probably plays a part. If reinfection does occur, it is not clear whether this has anything to do with developing into a persistent infection. While most women with HPV recover and do not develop cervical cancer, an individual is 13 times more likely to develop a high-grade squamous intraepithelial lesion (HSIL) from a persistent infection. From here, $\frac{1}{3}$ to $\frac{2}{3}$ of women with HSIL will go on to develop cervical cancer if the HSIL is not treated [25].

1.2 Human Papillomavirus: Mathematical Modelling Information

Mathematical modelling of biological situations has been done for centuries, with evidence from as early as the 11th and 12th centuries confirming that attempts were made to describe a biological situation in mathematical terms [29, 30]. From these early days, the use of mathematics in aiding our biological understanding has grown tremendously. One area in which mathematical modelling has proved very useful is that of epidemiology, modelling the spread of a disease through a population. It has been used to great effect in many situations and can be used in both a descriptive and predictive role [31]. In particular, sexually transmitted infections (STIs) have generally been of modelling interest - they have some very specific characteristics that need to

be considered, such as separation of genders, or contact structure. These ideas have been widely used, for example, in modelling human immunodeficiency virus (HIV) in populations, and comparing this to the effect of introducing an (as yet hypothetical) vaccine into the population. These ideas can also be applied to the situation with HPV, as described above.

Models relating to the transmission of HPV and the success of the vaccine are the subject of this section. Hughes *et al.* (2002) [32] comprises two models:- one examines the transmission of HPV in a population, the development into cancer (this is an ODE model), and the effect of the vaccine; the other looks at the effect of reducing cervical intraepithelial neoplasia (CIN) and (cervical) cancer through the use of the vaccine, which is an ODE/PDE model. They employ the use of different sexual activity groups as a means of dividing the population, a concept that other models also use. Whether the vaccine reduces susceptibility, transmissibility of disease or mean duration of infectiousness is considered. The models assume an arbitrary age at which people enter the susceptible class, i.e. an arbitrary age at which they become sexually active. They find that if the vaccine protects against -16 and -18, other high-risk types will fill the gap and so cancers caused by them will increase. They assume a mean immunity of 10 years with a vaccine that is 75% effective. The conclusion is that vaccinating women is about 75% as effective as vaccinating men and women, but this again may need to be checked against what is now known about the vaccine [32].

Many of the other models touch on slightly different aspects; Kohli *et al.* (2007) [33] use a Markov process model to assess the impact of vaccination, carrying it through to consider the effect on CIN and cervical cancer. The conclusions they reach suggest that 100% coverage of pre-teenage girls could lead to around a 75% drop in deaths from cervical cancer, but that the benefits of vaccination would decrease as the age of vaccination increased. Goldie *et al.* (2003) [34] use a computer-based simulation model to assess the effect of vaccination on the prevalence of HPV and pre-cancerous stages. This model again uses Markov processes to model the situation. Under certain assumptions, this model shows that a vaccine administered at age 13, even with differing efficacy levels, could have a significant effect on the incidence of cervical cancer. They also find that the proportion vaccinated is a key factor in the overall reduction of cervical cancer. Barnabas *et al.* (2006) [35] construct a compartmental, deterministic model dealing with infection of HPV and potential progression to cervical cancer. This model allows for an HPV sufferer to become immune. They assume a type-specific lifelong immunity once an individual has recovered, but allow for a 'gradual loss of a detectable antibody response', as tests may not be sensitive enough to detect very low levels of antibodies, and this assumption therefore allows for a comparison with test results. The

model also divides the population into age groups with a 5 year spread (i.e. 0-4yrs, 5-9yrs etc), and also into sexual activity groups (four groups relating to the rate at which an individual changes their sexual partner). The model is studied numerically, as the population is divided into a large number of different classes. Their results are similar to other conclusions, in that vaccinating men made very little difference, and what was important was vaccinating the girls before they became sexually active and achieving a high level of coverage. They did, however, assume the vaccine would offer lifelong protection, or that it would be supplemented with boosters, so if this assumption does not hold, the results could be quite different. Llamazares and Smith? (2008) [36] is the only paper explicitly to include a compartment for non-sexually active individuals, although it focuses on female-only vaccination, so does not mirror this with an equivalent non-sexually active male class. They concentrate on the impact of the efficacy and 'take' of the vaccine on the overall success of the vaccine.

The second part of the thesis relates to the most cost-effective way to introduce the vaccine, and indeed whether vaccination is cost-effective. A comparison of the current cost-effectiveness analyses suggests that the important assumptions are those such as the effectiveness of the vaccine, smear tests and the model used for predictions. Expansions to the models include ideas such as different options in using the vaccine and epidemiological variables. The vaccine cannot replace screening, as types -16 and -18 only account for about 70% of cervical cancer. In the USA there is a high cost to screening as they use expensive testing methods and screen frequently [22], so the vaccine along with a reduction in the screening programme may benefit them. Cost-effectiveness analyses often include reduced quality of life as a cost, although this value could be underestimated if aspects such as the effect the illness and treatment has on the rest of the family are not included. Although all models produce slightly different conclusions, the general consensus is that the vaccine is cost-effective under certain conditions [12, 22, 37]. It is agreed that screening will still be necessary, so this is taken into account. Most of the studies agree that there is little extra benefit in vaccinating males as well as females, and that a catch-up programme is probably not particularly cost-effective. Kim *et al.* (2007) [38] look at the effect of vaccinating males as well as females, specifically in Brazil. This study found that, even with vaccination of males (pre-adolescents), there was very little overall benefit. Cervical cancer rates would drop slightly in this situation, but the drop was marginal compared to the increased cost of vaccination. Indeed, the paper concludes that, if a choice must be made between vaccinating boys or increasing the level of vaccination in females, the latter option should be taken first [38]. Taira *et al.* (2004) [39] use decision analysis software to model HPV transmission dynamics, then assess the cost-effectiveness of including males in the

vaccination strategy. They also found that, although it is cost-effective to vaccinate the females, there is little benefit in also vaccinating males. However, they did show that under certain conditions, such as low vaccine coverage, or low vaccine efficacy, vaccinating males would be cost-effective [39]. Elbasha *et al.* (2007) [40] develop a dynamic model to consider cost-effectiveness and find that the inclusion of male vaccination would be cost-effective. Jit *et al.* (2008) [10] conduct a comprehensive economic evaluation, including many different scenarios, into introducing the HPV vaccine in the UK. They find that vaccination of 12 year old females is cost-effective under certain conditions, with a catch-up vaccination programme for females up to 18 years old initially. They do not find male vaccination to be cost-effective. These models were developed in the last few years, and include parameter assumptions that may not now be true. None of them employ optimal control as a means of judging cost-effectiveness; they mostly use decision analysis or stochastic processes.

From a study of the literature, we feel that a new approach would be to build a model that includes waning immunity and separate compartments for sexually active and non-sexually active individuals. We want to be able to consider the vaccination for both males and females, so our model allows for the inclusion of a protected male class. Following many other models [41], we model the disease as an SIS model as there are conflicting opinions about natural immunity. If protective natural immunity exists, its role is unclear (length of protection provided, proportion of individuals that develop immunity unknown) [41], so we also extend this to an $SIRS$ model to consider both cases.

1.3 Background Information: Age-structured Models

Developing age-structured models for infectious diseases is discussed at length in [31]. It often adds another level of accuracy to a model as behaviours (e.g. contact structures) and transmissibility of a disease can change as an individual ages. Age is usually introduced into a model as a variable, and is often combined with time as a variable to create a set of partial differential equations, as in [35, 42]. The inclusion of age as a variable allows many parameters, that would otherwise be constant in a time-dependent model, to be age-dependent. The models in [35, 42] also stratify their population into age groups, and calculate forces of infection that are dependent on these age groups.

Age-structured models are of particular use in modelling sexually transmitted diseases - sexual activity often varies significantly by age [3], and individuals usually contact others of a similar age [43]. We develop an age- and time-dependent system of PDEs in Chapter 6 to allow for the inclusion of age-dependent parameters, based on

data, that more accurately reflect the situation within society [3].

1.4 Background Information: Optimal Control

We use optimal control to assess the most cost-effective method of introducing the vaccination, both for the case of female-only vaccination and when both males and females are vaccinated. Optimal control is a useful mathematical tool which has previously been used to determine optimal vaccination strategies, although not for HPV. Lenhart and Workman (2007) [44] present many different biological situations which can be modelled using optimal control, including an epidemic model in a population. They also explain Pontryagin's Maximum Principle, which we use in Chapters 7 and 8 when developing our optimal control model. An explanation of this principle can be found in Chapter 7. Other authors [45, 46, 47, 48, 49, 50, 51, 52] have used optimal control in modelling epidemics, although only [52] use two control functions (something we introduce in Chapter 7). The types of control functions used in the cost function, or objective functional, vary between linear ('bang-bang') controls (in this scenario, the control is either at maximum or minimum, and can switch between the two states) and more complex functions, usually quadratic expressions. Quadratic expressions in the objective functional are commonly used, and we follow this trend in our formulation of the objective functional.

Behncke (2000) [46] considers general SIR and $SEIR$ models with different control strategies (e.g. vaccination/quarantine/screening). He uses a 'bang-bang' form of control and shows that the optimal solution (when considering vaccination) is to have maximum vaccination at early time. Sethi and Staats (1978) [47] analytically solve three different control scenarios using compartment models. They use the concepts of Pontryagin's Maximum Principle to characterise the optimal control solution, using 'bang-bang' controls. In doing this, they define the optimal control problems for three different types of intervention in compartment models and provide a useful reference when formulating a model with optimal control. Optimal control applied to an SIR model is taken further in [49], where an optimal control problem in a structured population is built. This model contains four connected subgroups, with an SIR model applied to each of them. Optimal control is applied to the model, with quadratic terms for the control functions in the objective functional, and Pontryagin's Maximum Principle is used to characterise the optimal control. Their results support other results found, namely that vaccination is highest at initial time, after which it decreases to very low levels. Gaff and Schaefer (2009) [50] use optimal control with different compartmental models (e.g. SIR, $SIRS$, $SEIR$) to discover whether the type of com-

partmental model used has an effect on the optimal strategy for minimising the number of infected individuals. They include both treatment and vaccination and vary the form of the objective functional. They show that the form of the compartmental model leads to only slight differences in the optimal strategy. They also find that vaccination is almost always indicated as part of any strategy. Zaman *et al.* (2008) [51] consider an SIR model with lifelong immunity for their optimal control problem and carry out stability analysis. Their work presents an optimal control problem where they seek to minimise the number of infected and susceptible individuals through vaccination, using a quadratic term for their control function in the objective functional. They use Pontryagin's Maximum Principle and show that, as in previous work, vaccination should be introduced at maximum levels, before decreasing over time. By introducing vaccination in this way, they show that the numbers of susceptibles and infecteds decrease to very low levels over a period of 90 days. Yan and Zou (2008) [52] apply optimal control to a compartmental model for Severe Acute Respiratory Syndrome (SARS). They consider two different interventions - quarantine and isolation - and search for both an optimal and sub-optimal solution (their sub-optimal solution is found by defining the form of the control function and looking to minimise the objective functional for that particular form). Their results for the control functions agree with the work discussed above - both the optimal and sub-optimal forms should be introduced at their maximums and decreased over time, which can greatly reduce the number of infected individuals. They also set both control functions as constants in their model and compare the results. In doing this, they found that there are a much greater number of infected individuals under the constant control model, with a much greater cost associated with this model.

In applying optimal control to our model, we considered the issues discussed in previous work. We decided to use optimal control to minimise the cost of vaccination, using two control functions (as in [52]). We also compared our optimal control solutions to the results generated from a constant control model, as in [52]. A precise explanation of our model can be seen in Chapters 7 and 8.

Optimal control as applied to PDEs is discussed in [44]. It is generally more complicated to apply optimal control to a PDE rather than an ODE, but it is possible to follow the ideas of Pontryagin's Maximum Principle provided an extra set of equations (the sensitivity equations) are also calculated. An example of this process takes place in Appendix A.

1.5 Thesis Structure

Chapter 2 introduces a simple model, divided into genders, that specifically looks at the impact of waning immunity from the vaccination. We consider the steady states of this system and compute numerical solutions. We also linearise the system, considering initial behaviour and what this can tell us about the full model.

Chapter 3 provides a description of the different parameters that will be used in subsequent Chapters. We discuss the data used to estimate these parameters and provide ranges for each parameter.

Chapters 4 and 5 introduce a model that incorporates both waning immunity and a non-sexually active class. Combining these with vaccination of non-sexually active individuals gives a more accurate picture of the impact of the vaccine. Chapter 4 presents this model as gender-free, a simplified version of the gender-present model presented in Chapter 5, that allows us to carry out further analysis. In both Chapters we find steady states and their stability, consider R_0 and the "effective" R_0 value (denoted here as R_0^e) and show numerical solutions to the system. In Chapter 5 we extend our SIS model to an $SIRS$ model to assess the effect any potential natural immunity has on the results.

Chapter 6 develops an age- and time-dependent PDE system for a very similar model to that presented in Chapter 5. In Chapter 6 we first consider this system at temporal equilibrium (so use a system of age-dependent ODEs), before progressing to the full PDE system. We consider how using a different force of infection impacts the results for the ODE and compare the results to the PDE.

Chapters 7 and 8 introduce optimal control. Chapter 7 uses a very similar model to that in Chapter 5 and applies optimal control to find the most cost-effective method of vaccination. Pontryagin's Maximum Principle is used to characterise the optimal control and numerical solutions are found. Chapter 8 shows optimal control applied to an age-dependent ODE model very similar to that seen in Chapter 6. For the ODE system of equations we characterise the optimal control and find numerical solutions. We refer to optimal control applied to a PDE model - the characterisation of optimal control functions subject to a PDE model can be seen in Appendix A.

For all numerical solutions presented we use Matlab. In Chapters 2, 4 and 5 we use the ODE solver provided by Matlab; numerical code used in Chapters 6, 7 and 8 is given in Appendix B.

Finally, we draw conclusions from this thesis and assess what new insights this work gives to the body of knowledge on prophylactic vaccination with waning immunity.

Chapter 2

Introductory HPV Model

2.1 Introduction

Mathematical modelling of infectious diseases can be done in many different ways. Throughout this thesis we consider our population as divided into 'compartments', with each compartment representing a different stage in the disease. Individuals move between different compartments at different rates and subject to various constraints (for example, females cannot move into compartments for male individuals). We are using this type of modelling at the population-level and as such it is the between-host dynamics that we are considering.

A basic model, first suggested by Kermack and McKendrick [53, 54, 55], is the SIR model and from this model, many other compartmental models can be derived. A common example is the $S \rightarrow I \rightarrow S$ model, which divides a population into two classes, susceptible and infected.

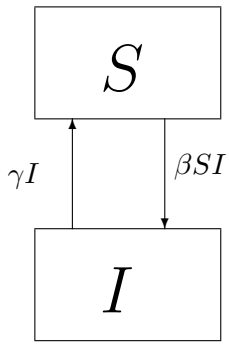


Figure 2-1: Schematic of a basic SIS system.

Individuals begin in (or enter the model through) the susceptible class (S). From there, they can move to the infected class (I) based on the 'force of infection', which is

calculated by multiplying the contact rate between susceptibles and infecteds, β, by I. Finally, individuals return from the infected class to the susceptible class with rate γ, the recovery rate. From this model (see Figure 2-1 for schematic) we can build a pair of differential equations to model the rate of change of each of the classes over time. The model equations are

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= -\beta SI + \gamma I, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI - \gamma I. \end{aligned} \tag{2.1}$$

In the first case, we assume that the duration of infection is very short compared to an individual's lifespan and so birth/ death rates are not included. As we can see from (2.1), these equations are modelling a closed population - if we set $N = S + I$, $\frac{\mathrm{d}N}{\mathrm{d}t} = \frac{\mathrm{d}(S+I)}{\mathrm{d}t} = 0$, which implies N is a constant. Once we have obtained this system (2.1), we can calculate the basic reproductive ratio R_0, which is defined as the

"average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible." (taken from [31], p.17)

For the disease to survive, and remain within a population, we require $R_0 > 1$ [31]. For $R_0 < 1$, the disease will die out [30]. For (2.1), $R_0 = \frac{\beta N}{\gamma}$. For more complicated models, it is appropriate to define the "effective" R_0 value (R_0^e); this is defined as the reproductive value for the system when factors exist that reduce the pool of susceptibles.

It is possible to find the steady states of (2.1). We calculate the steady states by allowing $t \to \infty$, so that $\frac{\mathrm{d}S}{\mathrm{d}t} = 0$ and $\frac{\mathrm{d}I}{\mathrm{d}t} = 0$. We then solve these equations for S^* and I^*, the steady states of the susceptibles and infecteds respectively. We find that there are two steady states - the first is the disease-free steady state $(S^*, I^*) = (N, 0)$. The second steady state is the disease-present steady state and is $(S^*, I^*) = (\frac{\gamma}{\beta}, N - \frac{\gamma}{\beta})$.

Once the steady states are determined, we can determine when they are stable using the Jacobian matrix. In this case, if the trace of the Jacobian is negative and the determinant is positive then the steady state in question is locally stable [30]. If both the trace and the determinant are zero, we consider the eigenvalues of the Jacobian to determine the stability of the steady state. We define $\frac{\mathrm{d}S}{\mathrm{d}t} = f(S, I)$ and $\frac{\mathrm{d}I}{\mathrm{d}t} = g(S, I)$, then the Jacobian matrix is

$$J = \begin{pmatrix} f_S & f_I \\ g_S & g_I \end{pmatrix}. \tag{2.2}$$

Calculating the Jacobian for (2.1) gives

$$J = \begin{pmatrix} -\beta I & \gamma - \beta S \\ \beta I & \beta S - \gamma \end{pmatrix}. \tag{2.3}$$

At steady state $(S^*, I^*) = (N, 0)$, the trace and determinant of (2.3) are zero, so we consider the eigenvalues. These are 0 and $\beta N - \gamma$, so we know that the disease-free steady state is stable for $R_0 < 1$ and unstable for $R_0 > 1$ (where $R_0 = \frac{\beta N}{\gamma}$). For the disease-present steady state $(S^*, I^*) = (\frac{\gamma}{\beta}, N - \frac{\gamma}{\beta})$, the same analysis shows that it is stable for $R_0 > 1$. This steady state does not exist for $R_0 < 1$. This analysis gives us some insights into the behaviour of the system - for $R_0 < 1$ the system will tend to the disease-free steady state, but for $R_0 > 1$ the disease-free steady state is unstable and so the system will tend to the disease-present steady state, which is stable when it exists in the positive quadrant.

Calculating and using the Jacobian matrix is a method of linearisation. Linearisation is used to simplify a model about a certain point (often a steady state) to allow for greater levels of analysis [30]. Comparing the linearised system to the full system can also indicate any underlying behaviours in the model that are maintained when the system is linearised.

Another aspect for consideration is the disease transmission: should it be frequency-dependent or density-dependent? The answer to this question will usually depend on the exact nature of the biological situation being modelled; here we are discussing a sexually transmitted infection, which suggests a frequency-dependent disease transmission [56]. For the models above, this would mean (in the simplest case) that instead of using βSI, we would use $\frac{\beta SI}{N}$.

All of the above analysis can offer insights into different aspects of the model and can allow us to make predictions based on the results - for example, we can predict whether or not an epidemic is likely and also estimate the final size of any possible epidemic. However, it is also important to note that the analysis will not always be straightforward, or even possible. We saw with the system above that it was not easy to find the stability of the steady states, and this system is one of the more basic. When building our model, there are further compartments we will need to include. As we are modelling a sexually transmitted disease, we will want to include both genders. We are interested in the effect of vaccination on the spread of the disease, and so we will need to include at least one protected class (dependent on whether we are vaccinating both males and females, or just females). As discussed above, the inclusion of further classes will mean that the use of R_0^e will be essential when considering the predictions of the model.

This chapter applies the above techniques to a five compartment model and as-

sesses the results. As mentioned, we include vaccination (with a vaccine with limited duration of protection) in our model and so we are considering the effect of waning immunity. We vary some of the model parameters to establish their influence on the model, especially the proportion of individuals vaccinated. We will concentrate on introducing many of the ideas and techniques we will employ throughout the thesis. We will introduce a deterministic, compartmental, population-level model for a sexually transmitted disease (in this case HPV) and analyse it to study its behaviour. We also study the effects of different parameters on the model to determine which ones have the greatest influence on the overall behaviour of the system. We reduce our five-equation system to a linearised two-equation system to consider the initial, underlying dynamics of the model.

2.2 Setting up the Model

Here we present a compartmental, deterministic model designed to represent a sexually active population (divided into males and females) with a protected female class (i.e. those females who have been vaccinated and so are immune at time $t = 0$). We include waning immunity in the model, so females who slowly lose their immunity join the susceptible class. Initially we are interested in the impact of a single vaccination event at time $t = 0$, which corresponds to monitoring a single population cohort of which a fraction are initially vaccinated. We are only considering a heterosexual population here. A schematic of the model can be seen in Fig. 2-2.

For the model, we assume a closed population with a 50:50 sex ratio, so $N = I_F + S_F + P_F = I_M + S_M$ gives our population size as $2N$. One parameter that shows a significant degree of variation is the average length of infection. From the literature [17, 28], we find this to be between 6 months and two years. As we are taking our time units to be in years, (with $\gamma_i = 1/(\text{average length of infection})$) we set $0.5 \leq \gamma_i \leq 2$, where $i = F, M$ (females, males). It could be argued that this range deals mainly with the more persistent infections, but many of the studies do not test females more frequently than every six months so we cannot really use a lower value. The average number of contacts per unit time is z_i. We vary this between 2 and 3 in our numerical solutions [3]. Finally, we assume $\alpha_F \approx 0.1$ is the rate at which protection is lost (corresponding to a 10 year efficacy for the vaccine). We also assume that transmission rates differ between males and females, so we take $\beta_{MF} \approx 0.6$ to be the transmission from males to females, and $\beta_{FM} \leq 0.6$ to be the transmission rate from females to males. These values come from estimates found in the literature that suggest transmission rates vary between 0.4 and 0.8 [28, 35, 40, 57]. We take our initial

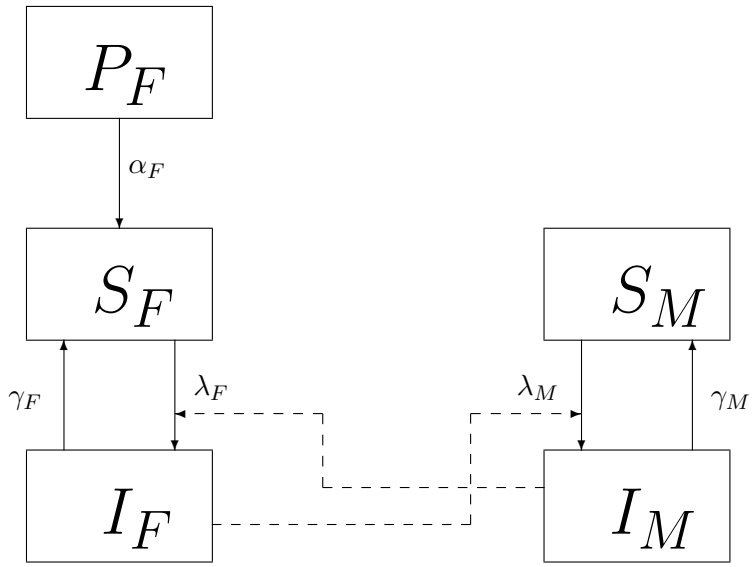


Figure 2-2: Schematic of the system. Note that $\lambda_F = \beta_{MF} z_F S_F \frac{I_M}{N}$ and $\lambda_M = \beta_{FM} z_M S_M \frac{I_F}{N}$.

conditions to be $S_M(0) = S_m^0$, $I_M(0) = I_m^0 = N - S_m^0$, $I_F(0) = I_f^0$, $P_F(0) = pN$ and $S_F(0) = (1-p)N - I_f^0$, where p is proportion vaccinated. With these parameters and initial conditions, our model becomes

$$\frac{\mathrm{d}P_F}{\mathrm{d}t} = -\alpha_F P_F, \tag{2.4a}$$
$$\frac{\mathrm{d}S_F}{\mathrm{d}t} = -\beta_{MF} z_F S_F \frac{I_M}{N} + \gamma_F I_F + \alpha_F P_F, \tag{2.4b}$$
$$\frac{\mathrm{d}I_F}{\mathrm{d}t} = \beta_{MF} z_F S_F \frac{I_M}{N} - \gamma_F I_F, \tag{2.4c}$$
$$\frac{\mathrm{d}S_M}{\mathrm{d}t} = -\beta_{FM} z_M S_M \frac{I_F}{N} + \gamma_M I_M, \tag{2.4d}$$
$$\frac{\mathrm{d}I_M}{\mathrm{d}t} = \beta_{FM} z_M S_M \frac{I_F}{N} - \gamma_M I_M. \tag{2.4e}$$

2.2.1 R_0

From here we can easily calculate the R_0 value of the system. We need to establish the number of secondary infections in females caused by the introduction of one infected female into a completely susceptible population (or similarly for males). For a female to be infected by another female, a male must be infected as an intermediate stage (as the infection needs to pass from a female to a male, and then to another female). We assume that one generation of infection is measured as female infection to female infection. As such, R_0 for this system is

$$R_0 = \frac{\beta_{MF} z_F}{\gamma_F} \frac{\beta_{FM} z_M}{\gamma_M}. \tag{2.5}$$

For $R_0 < 1$, this means that $\beta_{MF} z_F \beta_{FM} z_M < \gamma_F \gamma_M$.

2.3 Analysis

2.3.1 Reducing the System

As (2.4) is a closed system, we can reduce it to 3, or even 2, equations to make it easier to analyse. In doing so, our system of equations becomes

$$\frac{\mathrm{d}P_F}{\mathrm{d}t} = -\alpha_F P_F, \tag{2.6a}$$

$$\frac{\mathrm{d}I_F}{\mathrm{d}t} = \beta_{MF} z_F \frac{(N - I_F - P_F) I_M}{N} - \gamma_F I_F, \tag{2.6b}$$

$$\frac{\mathrm{d}I_M}{\mathrm{d}t} = \beta_{FM} z_M \frac{(N - I_M) I_F}{N} - \gamma_M I_M. \tag{2.6c}$$

We can now analyse the model as follows:- firstly we solve (2.6a) and then look at the stability of the steady states from the remaining two equations ((2.6b) and (2.6c)), and secondly we linearise the system, turning it into a vector equation of the form $\dot{\mathbf{x}} = A\mathbf{x}$, making it easier to solve.

2.3.2 Steady States and their Stability

We can look at the steady states of the three-equation system (2.6) and see what information these give. We can see that $P_F^* = 0$, so that leaves us with the two equilibrium equations for I_F^* and I_M^*. These are

$$\beta_{MF} z_F (N - I_F^*) \frac{I_M^*}{N} - \gamma_F I_F^* = 0, \tag{2.7a}$$

$$\beta_{FM} z_M (N - I_M^*) \frac{I_F^*}{N} - \gamma_M I_M^* = 0. \tag{2.7b}$$

These lead to two steady states - either the disease-free steady state $(I_F^*, I_M^*) = (0, 0)$, or the disease-present steady state, which is

$$(I_F^*, I_M^*) = \left(\frac{N(\beta_{MF}\beta_{FM} z_M z_F - \gamma_M \gamma_F)}{\beta_{FM} z_M (\beta_{MF} z_F + \gamma_F)}, \quad \frac{N(\beta_{MF}\beta_{FM} z_M z_F - \gamma_M \gamma_F)}{\beta_{MF} z_F (\beta_{FM} z_M + \gamma_M)} \right). \tag{2.8}$$

For the disease-present steady state to be realistic it must be positive, and we can see from (2.8) that it is positive when $R_0 > 1$.

We can calculate the stability of the steady states from the Jacobian; this is

$$\mathbf{J} = \begin{pmatrix} -(\frac{\beta_{MF} z_F I_M^*}{N} + \gamma_F) & \beta_{MF} z_F (1 - \frac{I_F^*}{N}) \\ \beta_{FM} z_M (1 - \frac{I_M^*}{N}) & -(\frac{\beta_{FM} z_M I_F^*}{N} + \gamma_M) \end{pmatrix}, \tag{2.9}$$

which at $(0, 0)$ tells us that the disease-free steady state is stable if

$$\gamma_M \gamma_F > \beta_{MF} \beta_{FM} z_F z_M. \tag{2.10}$$

The Jacobian tells us that the disease-free steady state is stable (i.e. $\det(J) > 0$ and $\mathrm{tr}(J) < 0$) as long as the disease-present steady state does not exist (i.e. that $R_0 < 1$) but while the disease-present steady state exists, the disease-free steady state is unstable. We see that the disease-present steady state is stable as long as $R_0 > 1$, i.e. as long as it exists there is a transcritical bifurcation as R_0 increases through $R_0 = 1$.

2.3.3 Linearising the System

Our second attempt at analysing the system (2.4) is to linearise the system about the initial conditions for the case $\alpha_F = 0$ and consider the model initially to assess its behaviour. We assume that $I_F(0)$ and $I_M(0)$ are very small, and therefore that $S_F(0) = (1 - p)N$ and $S_M(0) = N$. We substitute these values for $S_F(0)$ and $S_M(0)$ into (2.4c) and (2.4e). As neither of these equations contain P_F, we do not need to include (2.4a) in the system. We are left with a pair of coupled ODEs to solve,

$$\frac{\mathrm{d}I_F}{\mathrm{d}t} = -\gamma_F I_F + (1 - p)\beta_{MF} z_F I_M, \tag{2.11a}$$

$$\frac{\mathrm{d}I_M}{\mathrm{d}t} = \beta_{FM} z_M I_F - \gamma_M I_M. \tag{2.11b}$$

We can write this as $\dot{\mathbf{x}} = A\mathbf{x}$, with $\mathbf{x} = (I_F \;\; I_M)^T$ and

$$A = \begin{pmatrix} -\gamma_F & (1 - p)\beta_{MF} z_F \\ \beta_{FM} z_M & -\gamma_M \end{pmatrix}. \tag{2.12}$$

"Effective" R_0 Value and Critical Parameter Values

We can use (2.12) to determine to which steady state the system will tend. As described in Section 2.1, if $\mathrm{tr}(A) < 0$ and $\det(A) > 0$ then I_F and I_M will tend to the disease-free steady state. For $\det(A) > 0$, we require

$$\gamma_F \gamma_M > (1 - p)\beta_{MF} \beta_{FM} z_M z_F, \tag{2.13}$$

As R_0 relates to the number of secondary infections in an entirely susceptible population, taking p into the equation gives us an updated condition on R_0. That is, we require $1 > (1-p)R_0$ for the system to tend to the disease-free steady state. This now takes into account that some of our population are vaccinated and provides us with an "effective" R_0 value, R_0^e, as described in the introduction. In this case, we can rewrite (2.13) as $1 > R_0(1-p)$, giving us

$$R_0^e = (1-p)R_0. \tag{2.14}$$

From (2.14) we can find a critical value of p when $R_0^e = 1$. For the disease to be removed from the population, we require

$$p > p^{crit} := 1 - \frac{1}{R_0}. \tag{2.15}$$

Both (2.14) and (2.15) are not new; they are established results that are widely used [31]. Condition (2.15) tells us the critical proportion of individuals that need to be vaccinated for the system to tend to the disease-free steady state. The basic reproductive value is very important here; for $R_0 < 1$, the system will tend to the disease-free steady state regardless of the value of p; but when $R_0 > 1$, the value of p will influence whether or not the disease can be eradicated from the population.

Solving the System

We can now determine I_F and I_M by finding the eigenvalues and eigenvectors of A. The eigenvalues are $(k = 1, 2)$

$$\lambda_k = \frac{-(\gamma_F + \gamma_M) \pm \sqrt{(\gamma_F - \gamma_M)^2 + 4(1-p)\beta_{MF}\beta_{FM}z_M z_F}}{2}, \tag{2.16}$$

leading to corresponding eigenvectors

$$\mathbf{x}_k = \begin{pmatrix} (\gamma_F - \gamma_M) \mp \sqrt{(\gamma_F - \gamma_M)^2 + 4(1-p)\beta_{MF}\beta_{FM}z_M z_F} \\ -2\beta_{FM}z_M \end{pmatrix} \tag{2.17}$$

From these, we know that our solution is

$$\mathbf{x} = c_1\mathbf{x}_1 e^{\lambda_1 t} + c_2\mathbf{x}_2 e^{\lambda_2 t}, \tag{2.18}$$

where c_1, c_2 are constants to be determined from the initial conditions ($I_F(0) = I_M(0) = 1$, or $\mathbf{x}(0) = \mathbf{1}$). On using the initial conditions, we find that

$$c_1 = \frac{-1}{4\beta_{FM} z_M} - \left(\frac{(\gamma_F - \gamma_M) + 2\beta_{FM} z_M}{4\beta_{FM} z_M \sqrt{(\gamma_F - \gamma_M)^2 + 4(1-p)\beta_{MF}\beta_{FM} z_F z_M}}\right), \tag{2.19}$$

and that

$$c_2 = \frac{-1}{4\beta_{FM} z_M} + \left(\frac{(\gamma_F - \gamma_M) + 2\beta_{FM} z_M}{4\beta_{FM} z_M \sqrt{(\gamma_F - \gamma_M)^2 + 4(1-p)\beta_{MF}\beta_{FM} z_F z_M}}\right). \tag{2.20}$$

This gives us the solutions for $I_F(t)$ and $I_M(t)$ when $\alpha_F = 0$;

$$I_F = c_1 \mathbf{x}_1^1 e^{\lambda_1 t} + c_2 \mathbf{x}_2^1 e^{\lambda_2 t}, \tag{2.21}$$

and

$$I_M = c_1 \mathbf{x}_1^2 e^{\lambda_1 t} + c_2 \mathbf{x}_2^2 e^{\lambda_2 t}. \tag{2.22}$$

2.4 Numerical Solutions

We solve numerically (2.21) and (2.22) and try to establish whether the numerical solutions can show any interesting behaviours demonstrated by the system. We look at the effect varying some of the parameter values has on the profile of I_F. Fig. 2-3 shows the effects of varying p on the size of I_F. We see that the greater the value of p, the smaller the proportion of infected female individuals.

Figure 2-4 shows the linearised system (2.11) for varying values of p. It shows that for certain values of p, the infected female class initially decreases, then increases whilst the infected male class initially increases. To consider this analytically, we solve

$$\frac{\mathrm{d}I_F(0)}{\mathrm{d}t} < 0, \tag{2.23a}$$

$$\frac{\mathrm{d}I_M(0)}{\mathrm{d}t} > 0, \tag{2.23b}$$

to find a condition for p. We find that the conditions that need to be satisfied are $\beta_{FM} z_M > \gamma_M$ and

$$p > \left(1 - \frac{\gamma_F}{\beta_{MF} z_F}\right). \tag{2.24}$$

We also solve (2.6) numerically. The aim of the numerical solutions is two-fold. We want to assess the effect of different parameter values on the model's behaviour and we also want to compare the reduced system (2.6) to the linearised system (2.11), to identify whether (2.11) accurately describes the system's behaviour. We vary p to see the effect that this has on the behaviour of the system, as with such a high

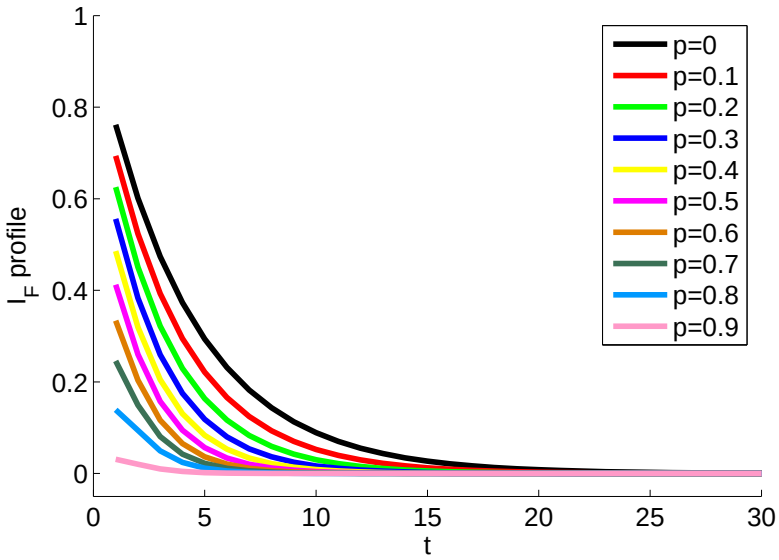
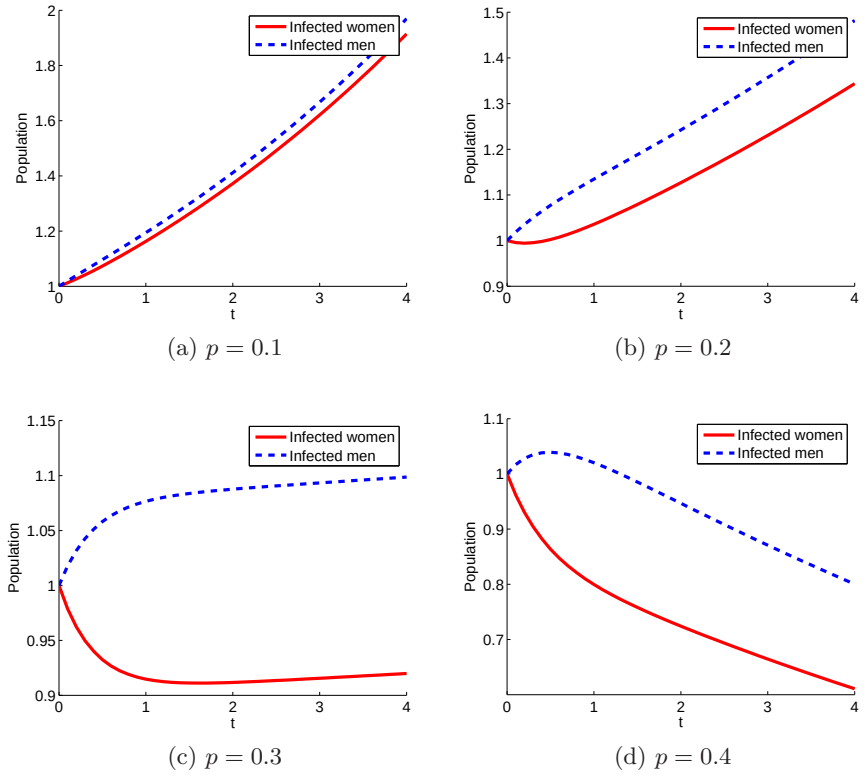


Figure 2-3: A graph showing the change in I_F as p varies. In this case we let $\gamma_F = 1.5$, $\gamma_M = 1$, $\beta_{MW} = 0.6$, $\beta_{WM} = 0.4$, $z_F = 2$, $z_M = 2$.

transmission rate we would expect (for this model) to need very high coverage levels. However, the analysis above tells us that the important parameters (based on R_0) are $\beta_{ij}, \gamma_i, z_i$ (where $i, j = M, F$). So even with low coverage levels, if the other parameters force $R_0 < 1$, the system tends to the disease-free steady state, whereas when $R_0 > 1$, we require the further condition of $1 > (1-p)R_0$, or $p > 1 - 1/R_0$ for the system to tend to the disease-free steady state.

This model can produce some interesting results. Figure 2-5 shows the varying class profiles when p is set at either 0.75 or 0.95 (high coverage levels), but with differing values of z_i and γ_i. In changing the values of γ_i, we also changed their relationship, so that in four of the graphs $\gamma_F > \gamma_M$, whereas in the other four, $\gamma_F < \gamma_M$. We see that z_i influences the size of the infected classes ($R_0 > 1$ for both $z_i = 2$ and $z_i = 3$, so we would not expect that varying this value alone would lead to eradication of the disease), as does varying γ_i. The change in γ_i leads to another change in behaviour, as the infected classes are much slower to increase for larger γ_i values.

Fig 2-6 shows the initial path of the I_i profiles from (2.6) when $p > (1-\gamma_F/\beta_{MF}z_F)$, which shows the I_M profile first increasing, then decreasing, and then finally increasing again. The I_F profile, meanwhile, decreases then increases. This is a solution of the reduced system, using the initial conditions $[P_F(0), I_F(0), I_M(0)] = [pN, 50, 50]$. We use $I_i(0) = 50$ as this shows the initial behaviour of the I_i classes more clearly than when $I_i(0) = 1$. The parameter values were chosen from within the ranges discussed



(a) $p = 0.1$ (b) $p = 0.2$

(c) $p = 0.3$ (d) $p = 0.4$

Figure 2-4: Plots of the linearised system as p increases. In all plots $\beta_{MF} = 0.6$, $\beta_{FM} = 0.4$, $z_F = z_M = 3$, $\gamma_M = 1$, $\gamma_F = 1.5$ and the initial conditions are $[1, 1]$.

above to ensure that p satisfied the condition $p > (1 - \gamma_F/\beta_{MF} z_F)$.

Figure 2-7 shows both the reduced system (2.6) and the linearised system (2.11) for small time, to compare their behaviours initially. We can see that, for $t \geq 10$, the two systems are not very similar, but that the two systems are very similar for $t \leq 1$.

2.5 Conclusions

We see fairly standard behaviour from the steady states and their stability, in that we have one disease-free steady state and one steady state where disease is present, with the disease-present steady state being stable as long as it exists. We see that it is possible to calculate a critical value of p for which the disease dies out, based on other parameters. In Chapter 3 we investigate parameter estimates based on available data, but by varying parameters in this model we are able to assess the amount of influence different parameters have on the overall behaviour of the model.

Figure 2-3 shows the numerical solutions for the solution of I_F found from (2.21).

It shows that increasing the proportion of individuals vaccinated will decrease the proportion of infected individuals.

Figure 2-4 shows the linearised system for varying values of p and we see that, for particular values of p, the initial profile of the male infected class increases, then decreases and initial female infected class decreases then increases. We find the condition on p for the female class to decrease initially and we see that when this is not satisfied, both classes increase initially. Satisfying (2.24) may mean that infection appears to be dying out initially, but will need to be monitored as it may increase at a later date.

Figure 2-5 shows the reduced system for a variety of parameter values. We see that both z_i and γ_i affect the eventual size of the infected classes and that the value of p only affects when the numbers of infected individuals begins to increase. A combination of small z_i values and large γ_i and p values shows the disease can be eradicated.

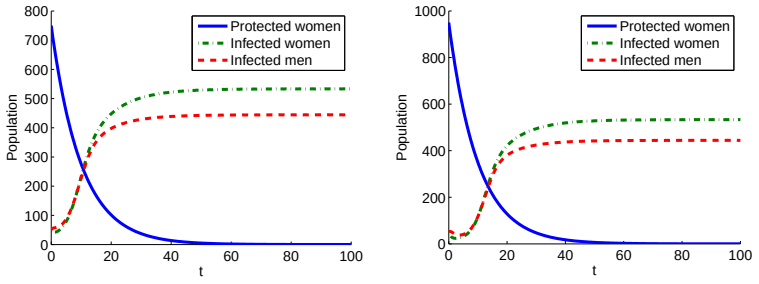
Figure 2-6 shows the reduced system initially. Although the initial conditions are different to those used for Figure 2-4d, the initial behaviour of the I_i classes in both Figures is the same. We suspect that we see this at small time because the initial behaviour of both the profiles is governed by satisfying (2.24) (so I_M increases and I_F decreases). However, the R_0 value for the system is greater than 1, so beyond the initial behaviour the infected classes start increasing.

We can now compare the results from the linearised system and the reduced system of three equations. The value of R_0 is the same in both systems. Equally, initial behaviour is the same for both systems. Figure 2-7 shows the two systems on the same graph to give us a direct comparison between the two. We can see that in both cases there is good agreement between the systems for $0 \leq t \leq 1$, but after that the two systems diverge and show quite different behaviour. Changing the values of the parameters did not affect the agreement between the two systems. As the linearised system is really only representative of the main system initially, this is an expected result.

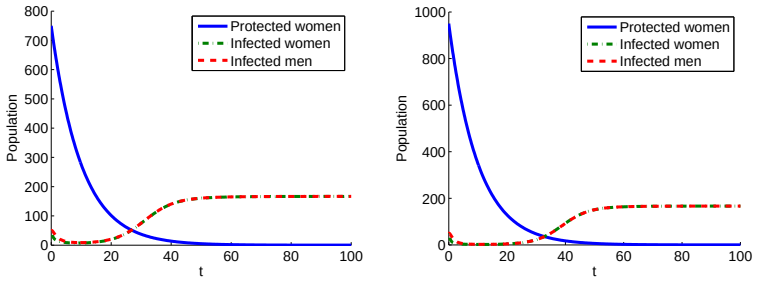
This model has been able to give some idea of how HPV would behave in the population from a very simplistic viewpoint. There are several limitations with the model; it does not include age-dependence, and in this type of situation, age-dependence could give more accurate results. We do not differentiate between sexually active and non-sexually active members of the population; this may play a role in determining the cost-effectiveness of the vaccine, and also the optimal age for the vaccine.

Nonetheless, we are able to draw some conclusions from this work. We can see that, under certain conditions, the vaccine will reduce the infective classes. In the linearised system, we can see that, even for low values of p, the vaccine will make a difference in the overall spread of infection (depending also on the value of R_0). The results for

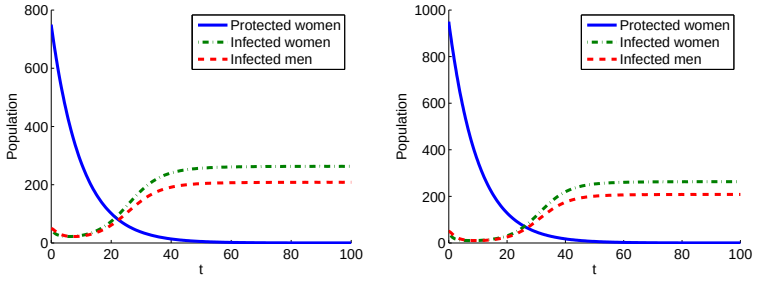
the linearised system are true for the case $\alpha_F = 0$, but for $\alpha_F \neq 0$ and $\alpha_F t << 1$, the inclusion of α would not have a dominant effect and so the similar conclusions would still hold. In the main system, we see that the emphasis is on the transmission probabilities, the average length of infection and the average number of contacts per unit time. The level of vaccination plays very little part here, although you may expect it to slow the epidemic, as it basically delays a proportion of the population becoming susceptible and therefore (potentially) infected. The level of the effect the vaccine can have will depend on the exact value of α_F; we know $\alpha_F < 0.2$ [18]. This value will determine the rate at which females lose their immunity and join the susceptible class.



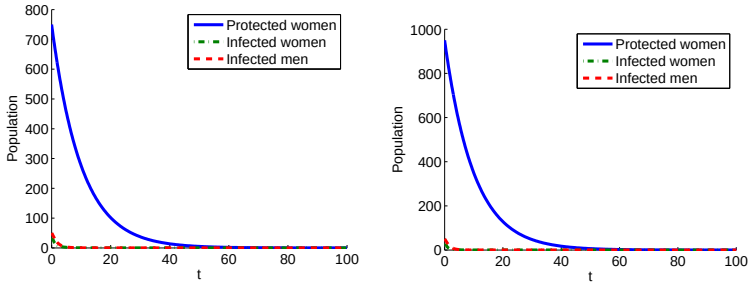
(a) $p = 0.75$ (b) $p = 0.95$



(c) $p = 0.75$ (d) $p = 0.95$



(e) $p = 0.75$ (f) $p = 0.95$



(g) $p = 0.75$ (h) $p = 0.95$

Figure 2-5: Eight graphs showing the effect of varying model parameters, with $\beta_{MF} = 0.6, \beta_{FM} = 0.4$ and $\alpha_F = 0.1$. Figures 2-5a, 2-5b, 2-5c and 2-5d have $z_i = 3$, with $z_i = 2$ in Figures 2-5e, 2-5f, 2-5g and 2-5h. In Figures 2-5a, 2-5b, 2-5e and 2-5f, $\gamma_F = 0.7$, $\gamma_M = 0.8$. In Figures 2-5c, 2-5d, 2-5g and 2-5h, $\gamma_F = 1.5$ and $\gamma_M = 1$. Initial conditions are $(pN, 50, 50)$.

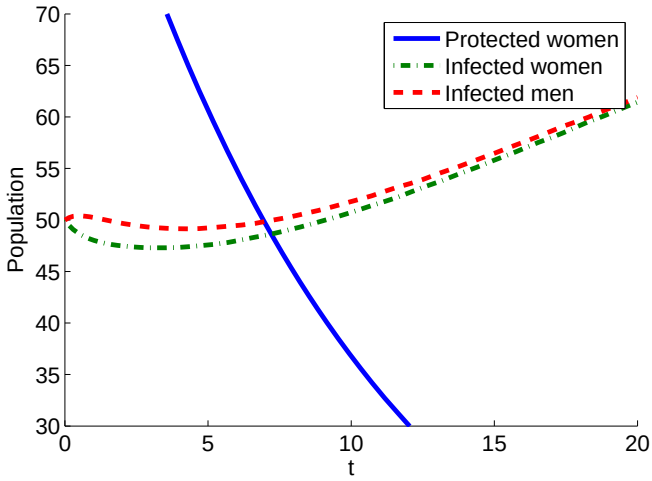


Figure 2-6: Showing the initial paths of the I_i profiles of the reduced system for $p = 0.1$, $\beta_{FM} = \beta_{MF} = 0.6$, $z_i = 2$, $\gamma_i = 1.1$, $\alpha_F = 0.1$ so that p satisfies $p > (1 - \gamma_F/\beta_{MF} z_F)$.

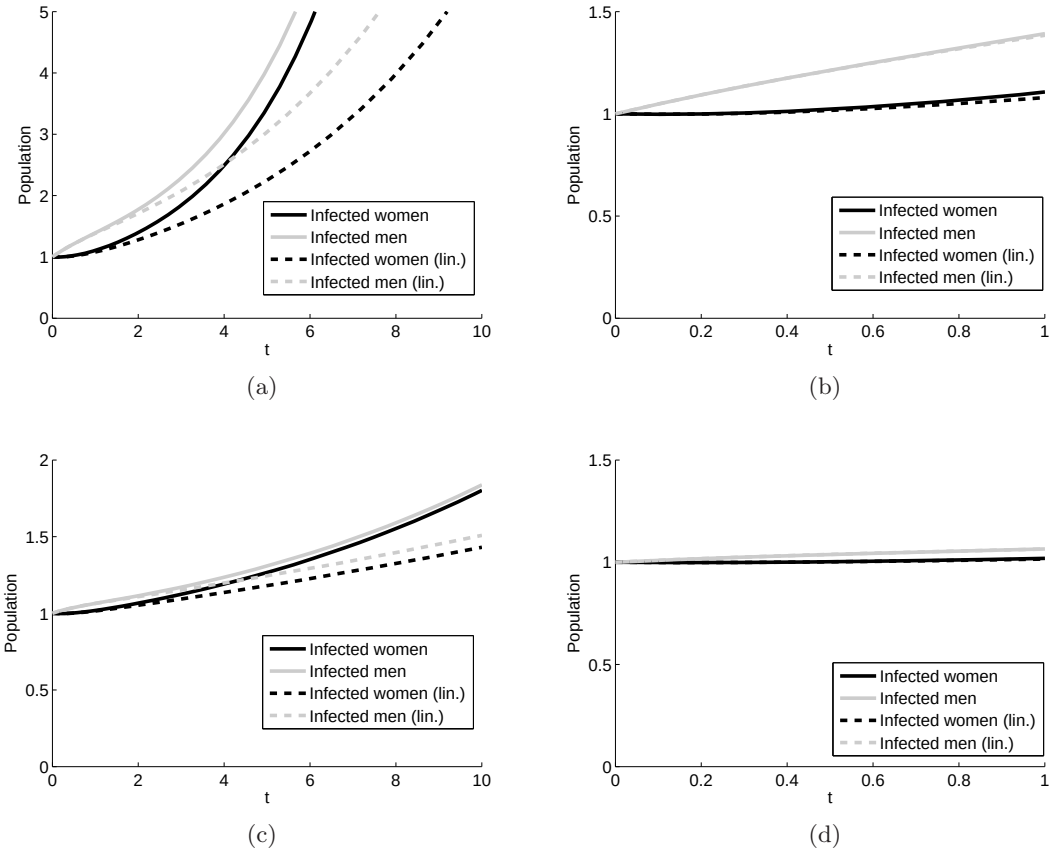


Figure 2-7: Comparing the reduced system and linearised system initially; the solid lines are the reduced system and the dashed lines are the linearised system. In all graphs $\beta_{FM} = \beta_{MF} = 0.6$, $z_i = 2$, $\alpha = 0.1$. In Figures 2-7a and 2-7b $\gamma_i = 0.7$ and $p = 0.45$. In Figures 2-7c and 2-7d $\gamma_i = 1.1$ and $p = 0.1$. In both pairs the right-hand graph is an enlargement of the left-hand graph. $P_F(t)$ is much larger than $I_i(t)$ initially and so is not shown.

Chapter 3

Determining the Parameter Values

In this Chapter we develop estimates, from data, of the parameters that we will use in subsequent chapters. In the following Chapters we develop compartmental, deterministic models that consist of a number of classes. A schematic of the model considered in Chapter 5 is given in Figure 3-1. This model contains all of the parameters that will be used in this thesis. The model here consists of seven classes, with males and females represented separately; female classes and parameters are denoted by a subscript 'F' and male classes and parameters by a subscript 'M'. The classes are: the protected (vaccinated) female class P_F, the non-sexually active classes J_i $(i = F, M)$, the susceptible (sexually active) classes S_i and the infected classes I_i. The force of infection, λ_i is defined as

$$\lambda_i = \frac{z\beta I_k}{(N_k - J_k)}, \qquad i, k = F, M, \quad i \neq k. \tag{3.1}$$

The definition of each of the parameters used in the model is given below. To estimate the different parameters we use data from various sources, making extensive use of the National Survey of Sexual Attitudes and Lifestyles II (NATSAL II), [3], carried out between 2000 and 2001 by the National Centre for Social Research. Many areas are covered in this survey, for example age at first intercourse, age of first partner, number of sexual partners in the last year. The parameters that need to be estimated are as follows:

- $\alpha(a)^{-1}$: Average length of vaccine protection.
- $\eta_i(a)^{-1}$: Average length of time spent in the non-sexually active class from the onset of the model $(i = F, M)$.

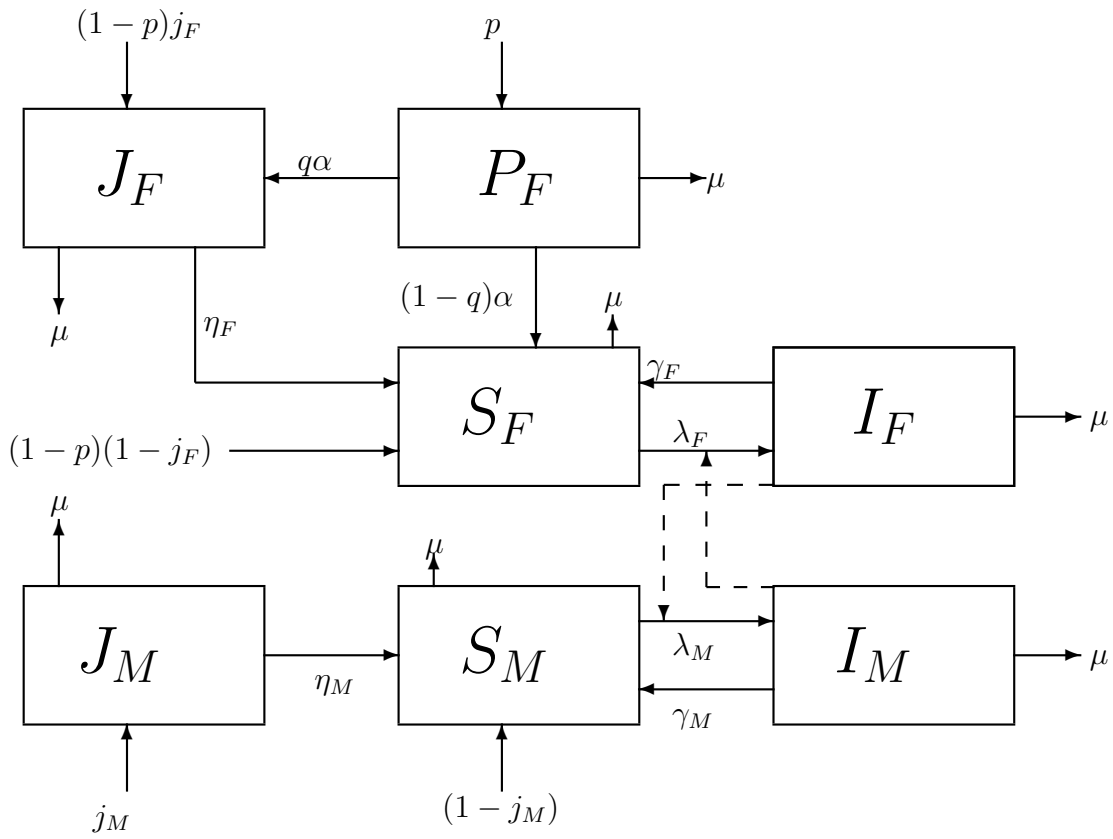


Figure 3-1: Schematic of model researched in Chapter 5. See text for further details.

- $q(\alpha)$: Proportion of protected class not sexually active when vaccine wears off.
- γ_i^{-1}: Average duration of infection.
- $z_i(a)$: Average number of sexual partners at age a per year.
- $\beta(a, a')$: Probability that someone of age a' infects someone of age a.
- j_i: Proportion of susceptible, non-sexually active at age a_0.
- p: Proportion of population to be vaccinated.
- $\mu(a)^{-1}$: Average lifespan.
- HPV incidence/prevalence in the UK (used for estimating the initial conditions for the age-dependent models).

3.1 $\alpha(a)^{-1}$: Average Length of Protection

It is difficult to determine an accurate estimate for this parameter, as the vaccines are so new that it is not yet known how long they will last. The latest information shows that vaccination provides protection after 5-6 years [58], so that $\alpha \leq 0.2$. The hope is that it will last at least 10 years, in which case $\alpha = 0.1$, but this will not be known for some time. We wish to predict $\alpha(a)$, assuming a linear relationship; assuming a vaccine with an average duration of 10 years,

$$\alpha(a) = 0.003a. \tag{3.2}$$

3.2 $\eta_i(a)$: Rate of becoming Sexually Active

To estimate $\eta_i(a)$, we calculated the rate at which individuals became sexually active using data from the NATSAL II survey [3]. When we do not include age-dependence, we estimated $\eta_i = 0.1$ (as $0.005 \leq \eta_i \leq 0.23$) [3].

To calculate $\eta_i(a)$, we first consider the steady state and assume (for the females) there is no vaccination. This gives (with J_i as given at the beginning of this Chapter)

$$\frac{\mathrm{d}J_i}{\mathrm{d}a} = -\eta_i(a)J_i. \tag{3.3}$$

The solution is calculated as

$$J(a) = J(a_0)exp\{-\int_{a_0}^{a} \eta_i(\tilde{a})\mathrm{d}\tilde{a}\}. \tag{3.4}$$

From the data, we can find the value of

$$x_{ik} := \frac{J(a)}{J(a_0)} = exp\{-\int_{a_k}^{a_{k+1}} \eta(\tilde{a})\mathrm{d}\tilde{a}\}, \tag{3.5}$$

$k = 0, ..., n, i = F, M$. If we take our integral limits to be consecutive years, and take η_{ik} to be constant in each of these intervals, then we can say that $-\log(x_{ik}) = \eta_{ik}$. We plotted $\eta_i(a)$ (calculated using NATSAL II data [3]), as can be seen in Figs. 3-2 and 3-3. It was possible to calculate the proportion that were sexually active at each age group from the database. For the youngest age group, η_i is the negative of the natural log of (1-proportion sexually active), but for all subsequent ages η_i was calculated by taking the negative of the natural log of (1-difference between the proportion sexually active for consecutive ages).

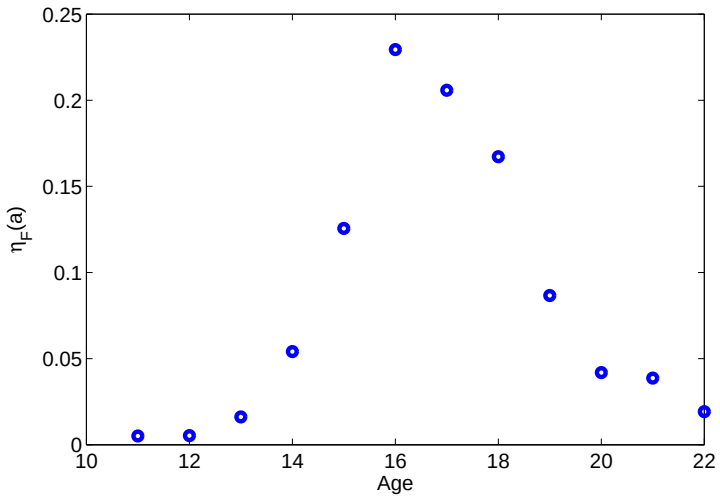


Figure 3-2: A graph showing the $\eta_F(a)$ data points against age.

From the distribution of the data, a normal distribution seems to be a potential fit, although only until the age $a \approx 19$. Beyond this, the data indicate that a normal distribution would not be the best fit, so we instead use piecewise continuous functions for both the $\eta_i(a)$. For $a_0 \leq a \leq 19$, we use a normal distribution for both $\eta_F(a)$ and $\eta_M(a)$. In both cases, the standard deviation used for the normal distribution is the standard deviation of the data, and the mean is estimated from the data. Once past $a \approx 19$, we set $\eta_i = 0.06$. Putting these together, our estimates for $\eta_F(a)$ and $\eta_M(a)$ are as follows:

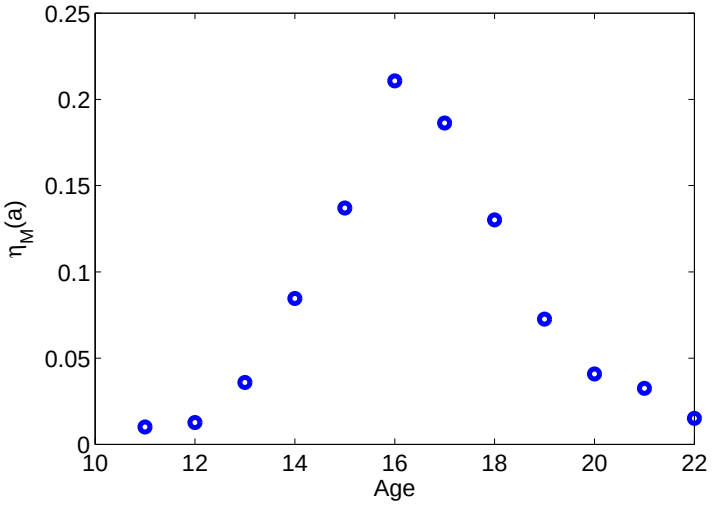


Figure 3-3: A graph showing the $\eta_M(a)$ data points against age.

$$\eta_F = \begin{cases} \frac{1}{1.33\sqrt{2\pi}} exp(-\frac{(x-16.95)^2}{2(1.33)^2}) & a \leq 19 \\ 0.06 & 19 < a \end{cases} \tag{3.6}$$

$$\eta_M = \begin{cases} \frac{1}{1.14\sqrt{2\pi}} exp(-\frac{(x-16.58)^2}{2(1.14)^2}) & a \leq 19 \\ 0.06 & 19 < a \end{cases} \tag{3.7}$$

3.3 $q(\alpha)$: Proportion of Protected who are Non-Sexually Active after Loss of Protection

Exactly what value $q(\alpha)$ takes will depend on the duration of induced protection. It can be estimated from looking at the data used for $\eta_F(a)$ (NATSAL II) [3], to see what percentage of females are non-sexually active at different ages. In Fig. 3-4, the proportion of sexually active girls is shown at each age, which was calculated by dividing the cumulative number of sexually active girls at age a by the total number of respondents at age a to the survey minus any girls of age less than a who were not sexually active. This is because those girls at age $a_1 < a$ may be sexually active by the time they reach age a and so should not be included.

From the data we see that the average value of $q(\alpha)$ over all ages settles down to $q(\alpha) \approx 0.1$, so we assume the area under $q(\alpha) = q = 0.1$ (for $0 \leq \alpha \leq 0.2$) to be the same as the area under $q(\alpha)$ for $0 \leq \alpha \leq 0.2$. We assume $q(\alpha)$ to be a function of the form

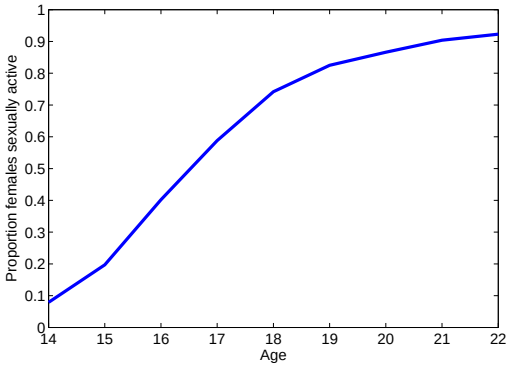


Figure 3-4: A plot of sexually active females against age.

$$q(\alpha) \approx \frac{m\alpha + 0.05}{1 + \alpha}. \tag{3.8}$$

Using these assumptions and available data, we find that

$$q(\alpha) \approx \frac{0.616\alpha + 0.05}{1 + \alpha}. \tag{3.9}$$

3.4 γ_i^{-1}: Average Duration of Infection

The average duration of an infection is hard to determine with any accuracy, as testing methods mean that it may not be clear from one test to the next whether it is the same infection being detected or a different one [17]. However, in most situations infection duration is cited as being between 6 months and 2 years [17, 28]. These tests are mainly carried out on women but we assume a similar average duration of infection for males [28]. This puts $\frac{1}{2} \leq \gamma_i \leq 2$. In the following Chapters, we take $\gamma_i \approx 1$.

3.5 $z_i(a)$: Average Number of Sexual Partners at Age a per Year

This parameter is estimated using data from NATSAL II [3]. The average values fall in the range $0.6 \leq z_i \leq 2.9$, and we use the estimate $z_i = 2$. For the age-dependent parameters when $a \geq 16$, we find a linear relationship from [3]. For $a < 16$, we calculate a linear relationship based on $z_i(0) = 0$ and the estimated values (from the linear relationship calculated using [3]) of $z_i(a)$ when $a = 16$. For simplicity in the age-dependent work, we assumed $z_F(a) = z_M(a)$; putting these assumptions together gives the function for $z_i(a)$ as

$$z_i(a) = \begin{cases} 0.1411a, & a \leq 16 \\ 2.93 - 0.042a, & 16 < a \leq 69 \\ 0. & a > 69 \end{cases} \tag{3.10}$$

3.6 $\beta(a, a')$: Probability Someone of Age a' Infects Someone of Age a

This can be divided up into βA, where β is the constant probability of transmission, and A is the contact structure between people of different ages [42]. Many papers refer to the transmission probability β. Most do not differentiate between male-female and female-male transmission, but all put $0.4 \leq \beta \leq 0.8$ [28, 35, 40, 32]. The most common estimate seems to be $\beta = 0.6$.

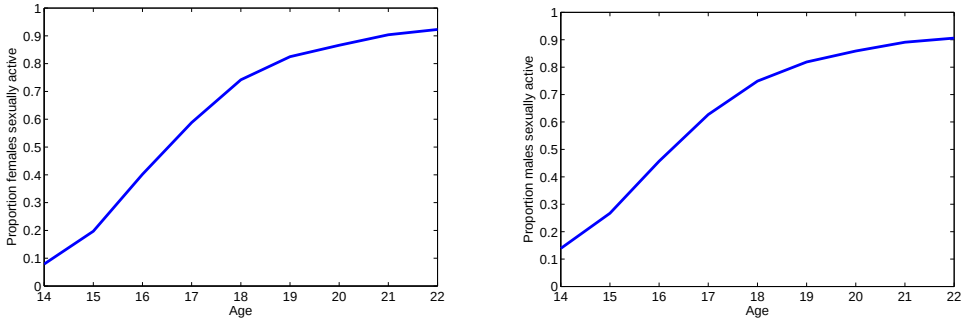
There are some papers that look at the sexual contact structure by age (A). Both of the references we have found are related to the United States [43, 59] and as there does not seem to be any data from the UK, these may provide the best information. Based on the information given in these papers, we see that the majority of individuals have partners very close to their own age. We therefore estimate

$$A = \begin{pmatrix} 0.5 & 0.25 & 0.25 & 0 & 0 & 0 & \dots & 0 \\ 0.25 & 0.5 & 0.125 & 0.125 & 0 & 0 & \dots & 0 \\ 0.125 & 0.125 & 0.5 & 0.125 & 0.125 & 0 & \dots & 0 \\ & \vdots & & & & & \vdots & \\ 0 & \dots & 0 & 0.125 & 0.125 & 0.5 & 0.125 & 0.125 \\ 0 & \dots & 0 & 0 & 0.125 & 0.125 & 0.5 & 0.25 \\ 0 & \dots & 0 & 0 & 0 & 0.25 & 0.25 & 0.5 \end{pmatrix}. \tag{3.11}$$

The entries in the matrix are the estimated probabilities of contact between individuals of age a and age $a^{'}$.

3.7 j_i: Proportion of Susceptible, Non-Sexually Active at Age a_0

This is a parameter that is only applicable in the time-dependent ODEs - it does not appear in the age-dependent ODE. That said, its value will depend on the age set as a_0, the age at which individuals enter the model. It can be estimated from the same data used for estimating $q(\alpha)$ and $\eta_i(a)$ [3].



(a) (b)

Figure 3-5: Plots of sexually active individuals against age. Figure 3-5a shows sexually active females and Figure 3-5b shows sexually active males.

In Figure 3-5 we have plotted the data as the sexually active proportion of the age group. The sexually active proportion was calculated by dividing the cumulative number of sexually active at age a by (total number of respondents at age a minus number not sexually active at age $a - a_1$), for all $a > a_1$. To give the non-sexually active proportion we can just take the sexually active proportion away from 1. From this information, we estimate $j_i = 0.9$ for $a \approx 12$.

3.8 p: Proportion Vaccinated

This is not a parameter to estimate, as we wish to investigate the effects of changing p on our model. That said, one would hope to achieve $p \approx 0.7$ in a vaccination programme [60].

3.9 $\mu(a)^{-1}$: Average Lifespan

From [61], we see that a Gompertz function is a good approximation for the death rate in England. From this article,

$$\mu_F(a) = 0.0000189e^{0.1a}, \tag{3.12}$$

and

$$\mu_M(a) = 0.0000347e^{0.098a} \tag{3.13}$$

Where we do not include μ_i as an age-dependent parameter, we set $\mu_i = 1/\phi$ $(i = F, M)$, with $\phi \approx 65$ being the average lifespan of an individual from age 12 [7].

Age	Manchester Cohort	Edinburgh and Lothian Cohort
<25	23.0	42.0
25-35	13.1	22.6
35-45	5.4	13.0
45-55	4.0	9.1
>55	1.8	5.4

Table 3.1: A comparison by age of percentages of women who are HPV positive. Data taken from [63] and [64].

3.10 HPV Incidence/Prevalence in the UK

This information is important to estimate the initial conditions for all our classes. There are three papers currently available that deal with HPV prevalence in the UK, looking at South Wales, Manchester and Edinburgh. All three studies show high prevalence in the younger age groups (15-24), with prevalence declining as age increases [62, 63, 64]. The results vary quite significantly. Here we will just discuss the Manchester and Edinburgh studies [63, 64].

As mentioned, there is significant difference between the two references. The Manchester cohort [63] has an HPV prevalence of $\approx 23\%$ for women aged under 25, whereas the Edinburgh and Lothian cohort returns a percentage of 42% for the under 25s. The Edinburgh and Lothian study [64] starts at a slightly older age (16.5 years) and has a higher maximum age (78 years) than the Manchester study (15 years and 69 years), but even allowing for this it is a big discrepancy. Both studies show a decline in HPV prevalence as age increases, although the percentages from the Edinburgh and Lothian cohort are still much larger than those from the Manchester cohort. These percentages can be seen in table 3.1. The Manchester study actually looked at the percentages over a 5 year age spread, but we have recalculated to bring them in line with those from the Edinburgh and Lothian cohort.

Using the Manchester cohort for our estimate we find that, over all ages, the average percentage of females infected is 7%, which we use in our initial conditions for our time-dependent ODEs. We fit a curve to the Manchester data to give initial conditions for the infected classes in our age- and time-dependent PDE model, the equation for which is given in Chapter 6.

A table of a standard set of parameter values, which we use in many of the following Chapters, is given in Table 3.2.

Parameter	**Symbol**	**Value Range**
Rate of losing protection	α	$\alpha \approx 0.1$
	$\alpha(a)$	$\alpha \approx 0.003a$
Rate of becoming sexually active	η_i	$\eta_i \approx 0.1$
	$\eta_M(a)$	$\eta_M(a) = \begin{cases} \frac{1}{1.14\sqrt{2\pi}} exp(-\frac{(x-16.58)^2}{2(1.14)^2}) & a \leq 19 \\ 0.06 & 19 < a \end{cases}$
	$\eta_F(a)$	$\eta_F(a) = \begin{cases} \frac{1}{1.33\sqrt{2\pi}} exp(-\frac{(x-16.95)^2}{2(1.33)^2}) & a \leq 19 \\ 0.06 & 19 < a \end{cases}$
Proportion of protected class not sexually active when vaccine wears off	$q(\alpha)$	$q(\alpha) \approx \frac{0.616\alpha+0.05}{1+\alpha}$
Average duration of infection	γ_i^{-1}	$\gamma_i \approx 1$
Average number of sexual partners per year	z_i	$z_i \approx 2$
	$z_i(a)$	$z_i(a) = \begin{cases} 0.1411a & a \leq 16 \\ 2.93 - 0.042a & 16 < a \leq 69 \\ 0 & 69 < a \end{cases}$
Probability of transmission of infection per sexual partner	β	$\beta \approx 0.6$
Proportion of the average population in one year that enters the 'juvenile' class	j_i	$j_i \approx 0.9$
Proportion of the average population in one year that is vaccinated	p	$0 \leq p \leq 1$
Average lifespan	$(\mu_i)^{-1}$	$\mu_i = 1/\phi$, $\phi \approx 65$
	$\mu_M(a)$	$\mu_M(a) = 0.0000347e^{0.098a}$
	$\mu_F(a)$	$\mu_F(a) = 0.0000189e^{0.1a}$

Table 3.2: Table of standard parameter values.

Chapter 4

Time-dependent Gender-free ODE Model

4.1 Introduction

Chapter 2 was an investigation into the spread of a disease through a population when vaccination was present. We initially introduced vaccination to a given proportion of the population and modelled its effects. However, a more realistic approach would be to consider a model that allows the population to renew itself. We therefore consider a model as shown in Figure 4-1, and look to answer certain questions. We are interested in the behaviour of this model - its steady states and R_0 value. We wish to know the effect of varying different parameters (behavioural or vaccination) as this can provide suggestions as to how to amend public health policy to best combat the disease. There have been several models suggested for HPV [35, 39, 65, 66]; a key element in ours is the introduction of a non-sexually active compartment which manifests itself through parameters such as the rate at which individuals become sexually active and the effect a non-sexually active class has on disease transmission.

The aim of this Chapter is to extend the work done in Chapter 2 with a more complex model. In the following chapter, Chapter 5, we present a model with genders, but for our initial study we do not include genders to reduce the complexity. We study the steady states and stability and discuss the "effective" R_0 value, R_0^e. A gender-free model in this situation can also be seen as modelling a population with both male and female vaccination, where there is both homosexual and heterosexual mixing.

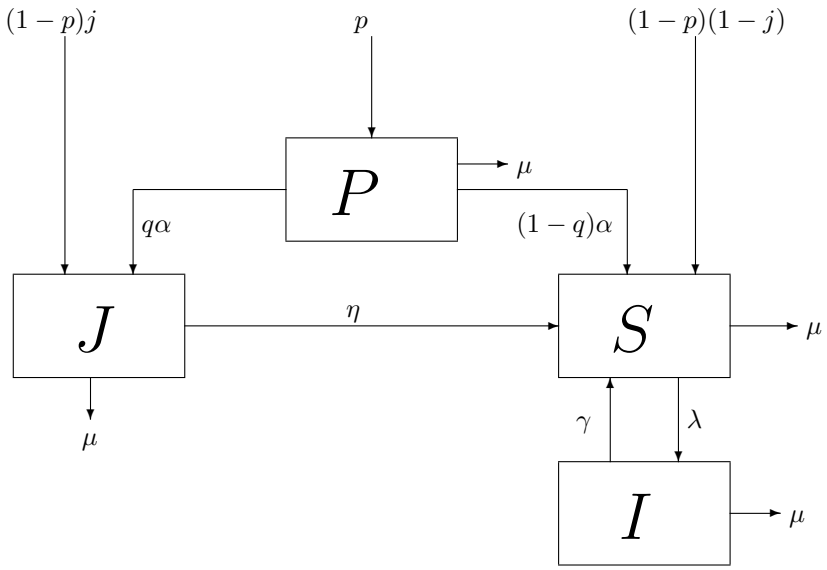


Figure 4-1: Schematic of the system.

4.2 Model

We build a compartmental model of a population, the schematic of which can be seen in Figure 4-1. It is a deterministic model, with parameters estimated as average values using age-dependent data (see Chapter 3). As the transmission probability, β, is so high, we follow [65] and assume homogeneous mixing. We do not account for heterogeneity in individual behaviour beyond classifying individuals as sexually active or inactive. In particular there is no sexual contact or age structure, neither do we distinguish genders. Although age structure is not included, behavioural parameter values were estimated from an age-dependent database (NATSAL II) [3]. Such simplifications allow us to highlight key parameter groupings such as the basic reproductive value R_0 and the "effective" reproductive value R_0^e from which the behaviour of HPV in a population with vaccination can be explored.

Vaccination takes place as individuals enter the model. We include a non-sexually active (juvenile) class, to allow us to consider the interplay between waning protection and onset of sexual activity. We present an SIS (susceptible-infected-susceptible) model, as in [34, 39, 67]. This produces a model with four classes; protected individuals P, juvenile individuals J, susceptible individuals (or susceptibles) S and infected individuals I. We assume that none of the cohort entering the model are infected, thus there is no external input into the I class. The parameters are as in Table 3.2 with

$\mu = \frac{1}{\phi}$ and the frequency-dependent force of infection λ is set as

$$\lambda = \frac{z\beta I}{(N-J)}. \tag{4.1}$$

Whilst the model here does not explicitly monitor the age of individuals, several parameters are directly linked to the age of vaccination. The proportion of individuals, $q(\alpha)$, who are not sexually active when the vaccination protection wears off and the proportion of unvaccinated individuals, j, who are not sexually active are both estimated using the NATSAL II database [3]. The parameter $q(\alpha)$ is taken to be an increasing function of α and was also estimated using data from [3]. Taking all of these factors into account, our model equations are

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \frac{pN}{\phi} - (\alpha + \frac{1}{\phi})P, \tag{4.2a}$$

$$\frac{\mathrm{d}J}{\mathrm{d}t} = \frac{(1-p)jN}{\phi} - (\eta + \frac{1}{\phi})J + q(\alpha)\alpha P, \tag{4.2b}$$

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \frac{(1-p)(1-j)N}{\phi} + (1-q(\alpha))\alpha P + \eta J - \frac{z\beta}{N-J}SI + \gamma I - \frac{1}{\phi}S, \tag{4.2c}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \frac{z\beta}{N-J}SI - (\gamma + \frac{1}{\phi})I. \tag{4.2d}$$

We determine R_0 for the system to be

$$R_0 = \frac{z\beta}{(\gamma + 1/\phi)}. \tag{4.3}$$

The initial conditions for this model are $P(0) = 0$, $J(0) = 25000$, $S(0) = 90750$ and $I(0) = 9250$, which are estimated using available data.

4.3 Analysis

4.3.1 Solving the Equations

We can solve (4.2a) and (4.2b) to give

$$P = \frac{pN}{\phi(\alpha + \frac{1}{\phi})}(1 - e^{-(\alpha+1/\phi)t}), \tag{4.4a}$$

$$J = \frac{C}{\eta + \frac{1}{\phi}} - \frac{De^{-(\alpha+1/\phi)t}}{\eta - \alpha} + Ee^{-(\eta+1/\phi)t}, \qquad \eta \neq \alpha, \tag{4.4b}$$

$$J = \frac{C}{\eta + \frac{1}{\phi}} - Dte^{-(\eta+1/\phi)t} + \tilde{E}e^{-(\eta+1/\phi)t}, \qquad \eta = \alpha, \tag{4.4c}$$

where

$$C = \frac{N}{\phi}[(1-p)j + \frac{q(\alpha)\alpha p}{\alpha + \frac{1}{\phi}}],$$
$$D = \frac{q(\alpha)\alpha p N}{\phi(\alpha + \frac{1}{\phi})},$$
$$E = \frac{-C}{\eta + \frac{1}{\phi}} + \frac{D}{\eta - \alpha} + J(0),$$
$$\tilde{E} = \frac{-C}{\eta + 1/\phi} + J(0).$$

The corresponding steady states are

$$P^* = \frac{pN}{\phi(\alpha + 1/\phi)}, \tag{4.5}$$

and

$$J^* = \frac{((1-p)(\alpha + 1/\phi)j + q(\alpha)\alpha p)N}{\phi(\alpha + 1/\phi)(\eta + 1/\phi)}. \tag{4.6}$$

These expressions (4.4) then feed into the nonlinear system for S and I;

$$\frac{\mathrm{d}S}{\mathrm{d}t} = (1-p)(1-j)\frac{N}{\phi} + (1-q(\alpha))\alpha P + \eta J - \frac{z\beta}{N-J}SI + \gamma I - \frac{1}{\phi}S, \tag{4.7a}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \frac{z\beta}{N-J}SI - (\gamma + \frac{1}{\phi})I. \tag{4.7b}$$

4.3.2 Steady States and Stability

From (4.7), we can find the two steady states (S^*, I^*). We know the values of P^* and J^* from above, so we set $S^* = N - P^* - J^* - I^*$ and hence solve $\frac{\mathrm{d}I}{\mathrm{d}t} = \frac{z\beta}{N-J^*}(N - P^* - J^* - I^*)I^* - (\gamma + \frac{1}{\phi})I^* = 0$, giving $(S^*, I^*) = (N - P^* - J^*, 0)$ (disease-free steady state) or $(S^*, I^*) = (\frac{N-J^*}{R_0}, (1 - \frac{1}{R_0})(N - J^*) - P^*)$ (disease-present steady state).

We can calculate the Jacobian for this system and use it to determine conditions for stability of the steady states. In particular, for a steady state to be stable, we require $\mathrm{tr}(A) < 0$ and $\det(A) > 0$. For the disease-free steady state the Jacobian is

$$\mathbf{B} := \begin{pmatrix} -\frac{1}{\phi} & \frac{-z\beta(N-P^*-J^*)}{N-J^*} + \gamma \\ 0 & \frac{z\beta(N-P^*-J^*)}{N-J^*} - (\gamma + \frac{1}{\phi}) \end{pmatrix}. \tag{4.8}$$

If

$$\frac{z\beta(N-P^*-J^*)}{N-J^*}-(\gamma+\frac{1}{\phi})<0 \tag{4.9}$$

then the disease-free steady state will be stable. Rearranging this condition we find

$$R_0(1-\frac{P^*}{N-J^*})<1. \tag{4.10}$$

Substituting for P^* and J^*, we find that the condition to be satisfied is

$$R_0(1-\frac{p(\eta+1/\phi)}{\phi(\eta+1/\phi)(\alpha+1/\phi)-((1-p)(\alpha+1/\phi)j+q(\alpha)\alpha p)})<1. \tag{4.11}$$

The Jacobian for the disease-present steady state of the system (4.7) is

$$\mathbf{B}:=\begin{pmatrix} \frac{z\beta P^*}{N-J^*}-z\beta(1-\frac{1}{R_0})-\frac{1}{\phi} & -\frac{z\beta P^*}{N-J^*}+z\beta(1-\frac{1}{R_0}) \\ -\frac{1}{\phi} & 0 \end{pmatrix}. \tag{4.12}$$

In this case, the disease-present steady state is stable if the condition given in (4.11) is not satisfied. This is also the condition that needs to be met for the disease-present steady state to exist, so we can say that as long as the disease-present steady state exists, it is stable. Furthermore, the disease-free steady state is only stable as long as the disease-present steady state does not exist; otherwise, it is unstable. This is a transcritical bifurcation.

We now plot part of the phase plane of this system about the steady states, using parameter estimates as detailed in Chapter 3 (see Table 3.2), which can be seen in Figure 4-2. It shows the situation when the disease-present steady state exists and we can see that in this scenario, the disease-free steady state is a saddle point and the disease-present steady state is a stable node.

4.3.3 "Effective" R_0 and Critical Values

Results presented above give us expressions for R_0^e, the "effective" R_0, as defined in Chapter 2. It is such that, for $R_0^e<1$, the disease-free steady state is stable and vaccination can eradicate infection from the population.

We have

$$R_0^e=R_0(1-\frac{p(\eta+1/\phi)}{\phi(\eta+1/\phi)(\alpha+1/\phi)-((1-p)(\alpha+1/\phi)j+q(\alpha)\alpha p)}).$$

Without a non-sexually active class, but with vaccination providing lifelong protection in a model, we would expect that $R_0^e=(1-p)R_0$ [30]. If we allow $j,q(\alpha)=0$ (as

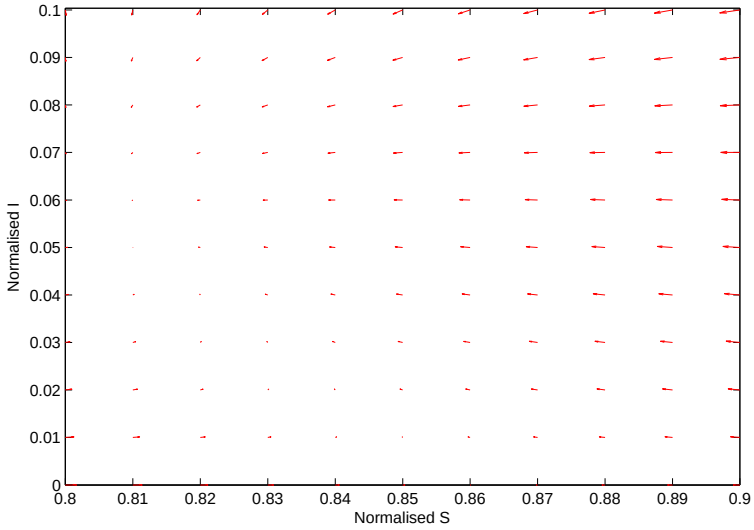


Figure 4-2: Phase plane of the system, using the standard parameter set as given in Table 3.2.

these are the parameters that relate to the non-sexually active class), but keep our assumption of waning immunity, we find that (as shown in [68])

$$R_0^e = R_0(1 - \frac{1}{\phi(\alpha + 1/\phi)}p). \tag{4.13}$$

The extra term in front of p relates to our assumption of waning immunity. If we assume protection is lifelong (i.e. set $\alpha = 0$) then $R_0^e = R_0(1-p)$, thereby agreeing with previous work, as discussed in [30].

Corresponding to $R_0^e = 1$, we can derive critical values for η and α for eradication of infection; these are

$$\eta^{crit} = \frac{(1 - \frac{1}{R_0})((1-p)(\alpha + 1/\phi)j + q(\alpha)\alpha p)}{\phi(\alpha + 1/\phi)(1 - \frac{1}{R_0}) - p} - \frac{1}{\phi},$$

and

$$\alpha^{crit} = \frac{p(\eta + 1/\phi) - (1 - \frac{1}{R_0})(\eta + \frac{1}{\phi} - \frac{(1-p)j}{\phi})}{(1 - \frac{1}{R_0})(\phi(\eta + 1/\phi) - (1-p)j) - q(\alpha^{crit})p}.$$

With $q(\alpha) = \frac{0.616\alpha+0.05}{1+\alpha}$, we obtain a quadratic for α^{crit};

$$(\phi(\eta+\frac{1}{\phi}) - (1-p)j - \frac{0.616p}{(1-1/R_0)})(\alpha^{crit})^2 + ((\phi(\eta+\frac{1}{\phi}) - (1-p)j)(1+\frac{1}{\phi}) - \frac{(p(\eta+\frac{1}{\phi}+0.05))}{(1-\frac{1}{R_0})})\alpha^{crit} - (\frac{p(\eta+\frac{1}{\phi})}{(1-\frac{1}{R_0})} - (\eta + \frac{1-(1-p)j}{\phi})) = 0, \quad (4.14)$$

which has solutions

$$\alpha^{crit} = \frac{-k \pm \sqrt{k^2 + 4(\phi(\eta+\frac{1}{\phi}) - (1-p)j - \frac{0.616p}{(1-1/R_0)})(\frac{p(\eta+\frac{1}{\phi})}{(1-\frac{1}{R_0})} - (\eta + \frac{1-(1-p)j}{\phi}))}}{2(\phi(\eta+\frac{1}{\phi}) - (1-p)j - \frac{0.616p}{(1-1/R_0)})}, \quad (4.15)$$

where $k = ((\phi(\eta+\frac{1}{\phi}) - (1-p)j)(1+\frac{1}{\phi}) - \frac{(p(\eta+\frac{1}{\phi}+0.05))}{(1-\frac{1}{R_0})})$. We now let $m = (\phi(\eta+\frac{1}{\phi}) - (1-p)j - \frac{0.616p}{(1-1/R_0)})$ and $n = (\frac{p(\eta+\frac{1}{\phi})}{(1-\frac{1}{R_0})} - (\eta + \frac{1-(1-p)j}{\phi}))$. If $m > 0$, $n > 0$ and $k < 0$, either solution given in (4.15) is positive. If $\alpha^{crit} < 0$, it means that the disease could be eradicated regardless of the duration of protection offered by the vaccine. For our standard parameter set, this is not the case and $\alpha^{crit} \approx 0.06$.

We can do the same to find a critical value for p, namely

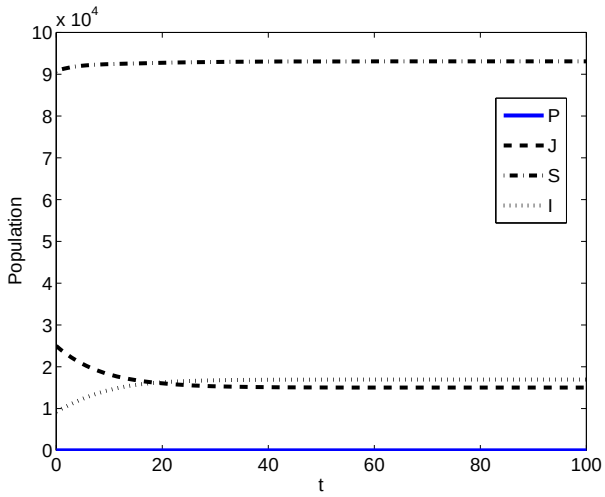
$$p^{crit} = \frac{[\phi(\alpha+1/\phi)(1-1/R_0)(\eta+(1-j)/\phi)]}{(\eta+1/\phi+(1-1/R_0)(\alpha(q(\alpha)-j)-j/\phi))}. \quad (4.16)$$

For $R_0^e < 1$, we require $p > p^{crit}$. This value ties in with the concept of "herd immunity" - i.e. that it is not necessary to vaccinate every individual in a population to eradicate a disease from that population [31]. This critical value of p is that proportion of individuals that it is necessary to vaccinate so that the disease dies out in the population. From the equation (4.16) we can see that, for $R_0 < 1$, $p^{crit} < 0$ - i.e. that there is no minimum level of vaccination required to eradicate the disease. When $R_0 > 1$, $p^{crit} > 0$ provided $(\eta + 1/\phi)(\frac{R_0}{R_0-1}) > (\alpha(j-q(\alpha)) + j/\phi)$. This gives us a relationship between the behavioural parameters (left hand side) and the vaccination parameters (right hand side).

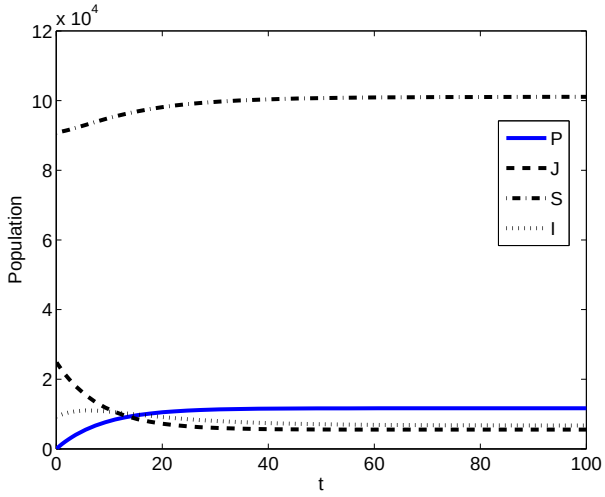
4.4 Numerical Solutions

As an exploration of the model, we used Matlab to solve (4.2). We tested it both with and without protection, to show the impact vaccination would have over time. Figure 4-3 demonstrates this; Figure 4-3a shows the numerical solution for the population when there is no vaccination taking place in the population. Figure 4-3b shows the case when $P(0) = 0$, but the proportion of individuals vaccinated is $p = 0.7$, and shows the infection being maintained in the population. Figure 4-4 shows the same set of graphs as in Figure 4-3, with the difference that $z = 1.7$. For this value of z, infection is at very low levels in the population without vaccination, and dies out when vaccination is present.

We also consider numerically the change in R_0^e when different parameters are varied. Figure 4-5 shows R_0^e against η for different values of α, so we are investigating how the duration of protection and the rate at which individuals become sexually active influences whether or not the disease dies out. Figure 4-5 shows that α has a much greater effect on R_0^e than η, and that we require $\alpha \leq 0.04$ for all values of η for $R_0^e < 1$.

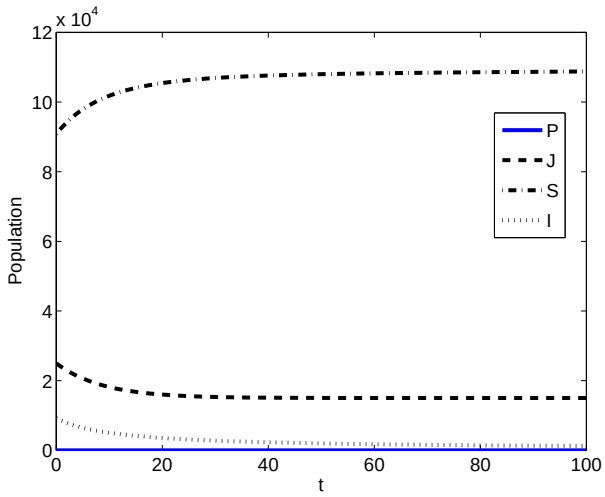


(a)

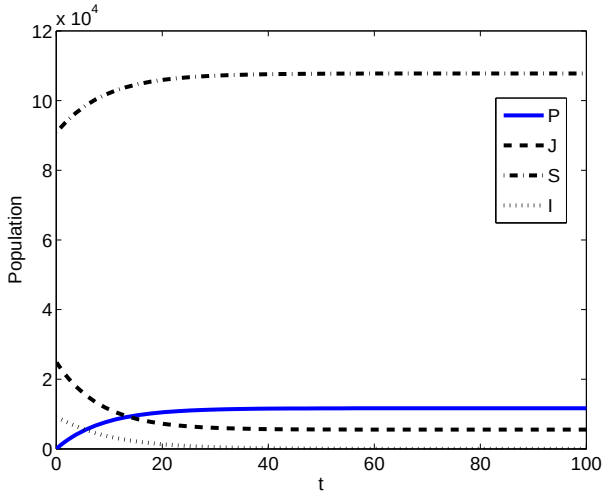


(b)

Figure 4-3: Numerical solutions to the gender-free, time-dependent ODE. All parameter values are the standard values given in Chapter 3.



(a)



(b)

Figure 4-4: Numerical solutions to the gender-free, time-dependent ODE. All parameter values are the standard values given in Chapter 3 barring z, which is set to $z = 1.7$.

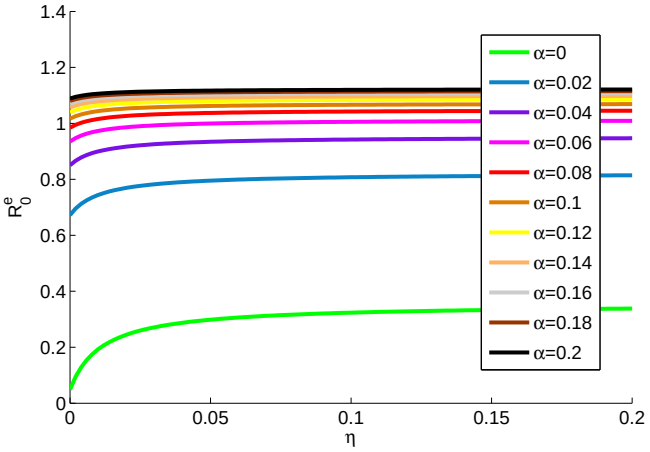


Figure 4-5: A graph showing the effect of varying η and α on the value of R_0^e. All other parameters are standard, as given in Table 3.2.

4.5 Conclusions

This time-dependent ODE model, with its non-sexually active class, better reflects the vaccination strategy (vaccination for a sexually transmitted infection occurs at a relatively young age) than the model presented in Chapter 2. We explore the model analytically, considering the steady states and their stability, and the influence of various parameters on the "effective" R_0 value, R_0^e. In presenting numerical solutions, we can, using our estimated parameter values, consider the behaviour of the model in different circumstances. We find that there are two steady states, with the value of R_0^e telling us which steady state the system will tend towards.

Changing the value of z from 2 to 1.7 gives different results, with Figure 4-4 showing that with no protection present, the disease remains in the population. Once protection is introduced, the model tends to the disease-free steady state. It demonstrates the influence that z has on the model (expected, as z is a dominant parameter in R_0).

Figure 4-5 shows how R_0^e varies based on changing values of α and η and demonstrates that a vaccine offering close to lifelong protection ($\alpha \in [0, 0.04]$) may well mean that the disease can be removed from the population, regardless of the value of η.

This Chapter has provided some insights into the behaviour of a gender-free model with vaccination. It shows the steady states and how different parameters influence which steady state the model will tend towards. It gives an excellent starting point for the following Chapter, when we will introduce genders to this model and assess the difference that this makes.

Chapter 5

Time-dependent ODE with Genders

5.1 Introduction

In this Chapter we introduce a compartmental, population-level, time-dependent ODE model with genders. As before, we find the "effective" reproductive value for HPV, R_0^e. We are interested in using R_0^e to assess the interplay of behavioural and vaccination parameters, and how these affect the potential success of the vaccine. We also use R_0^e to judge the impact of including male vaccination in the vaccination policy.

This complements previous work ([65, 66, 68], for example) and by using a simple structure, highlights key parameter groupings. These parameter groupings are critical in understanding how HPV could be contained in a population, by a vaccination strategy aimed either at females only prior to their sexual debut, or at both males and females.

The aim of this Chapter is to extend the work presented in Chapter 4 by including genders in the population model. The introduction of genders into a model is common when a sexually transmitted infection is being considered [31], as it is helpful to be able to model contact between genders and parameter values are often gender-dependent. The introduction of genders also allows us to consider female-only vaccination, which is the current policy for HPV [2]. We present an investigation into the influence the various behavioural and vaccination parameters have on our model, infection prevalence, and in particular on the value of R_0^e. We introduce male vaccination and compare this to the situation of female-only vaccination, looking at how the introduction of male vaccination affects the total number of individuals that need to be vaccinated in order to control the spread of the disease.

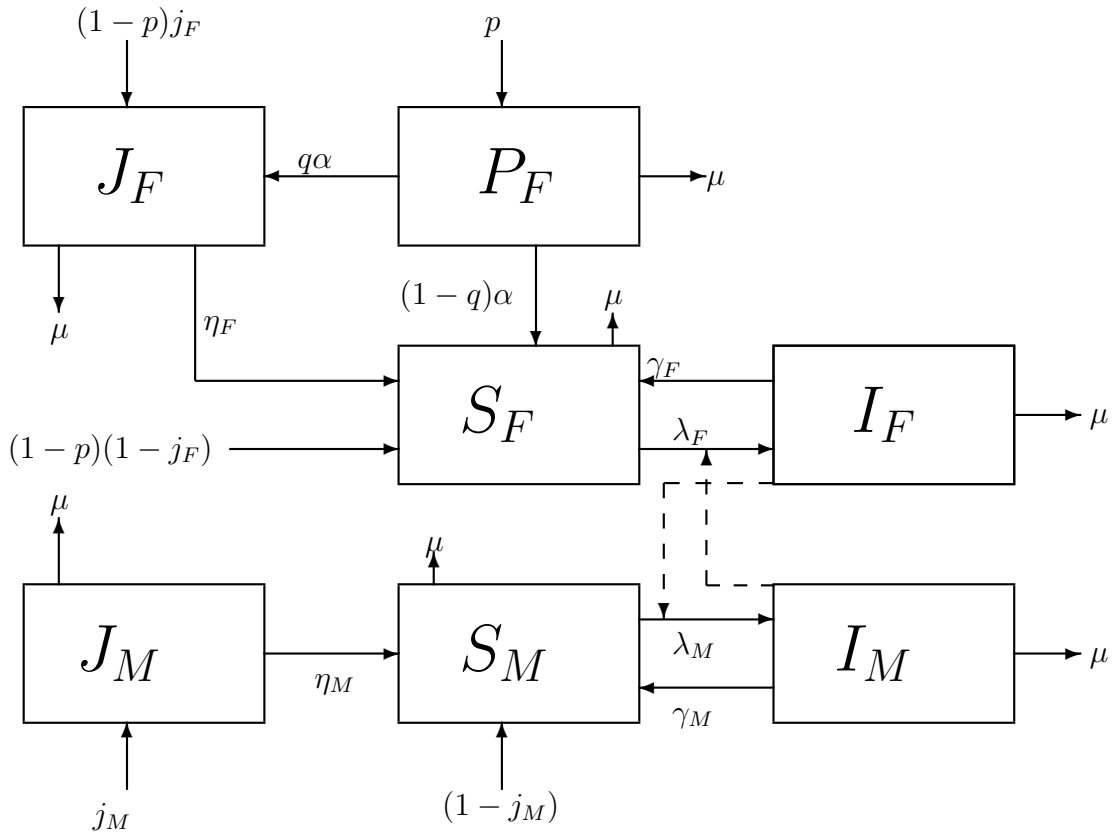


Figure 5-1: Schematic of model. See Table 3.2 for parameter definitions and text for further details.

5.2 Model

The model presented here is a continuation of the model presented in Chapter 4, as we now introduce genders to the model. The schematic of this model can be seen in Figure 5-1. A description of the parameters can be found in Chapters 3 and 4.

Considering HPV as a sexually transmitted infection (STI), we introduce two genders and study the heterosexual case. Initially we assume that only females are vaccinated, as this is current UK policy [2], and that vaccination takes place as individuals enter the model. As in Chapter 4, we include a non-sexually active (juvenile) class, to allow us to consider the interplay between waning protection and onset of sexual activity. We present an *SIS* (susceptible-infected-susceptible) model for the infection, as in [34, 39, 67]. This produces a model with seven classes; protected females P_F, juvenile individuals J_i, susceptible individuals (or susceptibles) S_i and infected individuals I_i. We assume that none of the cohort entering the model are infected, thus there is no external input into the I_i classes. Here $i = F, M$ represents females and males. The

parameters are as in Table 3.2; these estimates have a variety of published sources. The frequency-dependent force of infection λ_i is set as

$$\lambda_i = \frac{z\beta I_k}{(N_k - J_k)}, \qquad i,k = F,M, \quad i \neq k. \tag{5.1}$$

Age-related gender differences are included by assuming that the rate of becoming sexually active is greater for males than females ($\eta_M \geq \eta_F$) and that more males are sexually active than females when vaccination is administered ($j_M \leq j_F$). Taking all of these factors into account, our model equations are

$$\frac{\mathrm{d}P_F}{\mathrm{d}t} = p\frac{N_F}{\phi} - (\alpha + \frac{1}{\phi})P_F, \tag{5.2a}$$

$$\frac{\mathrm{d}J_F}{\mathrm{d}t} = (1-p)j_F\frac{N_F}{\phi} - (\eta_F + \frac{1}{\phi})J_F + q(\alpha)\alpha P_F, \tag{5.2b}$$

$$\frac{\mathrm{d}S_F}{\mathrm{d}t} = (1-j_F)(1-p)\frac{N_F}{\phi} + (1-q(\alpha))\alpha P_F + \eta_F J_F - \frac{z\beta}{N_M - J_M}I_M S_F + \gamma_F I_F - \frac{1}{\phi}S_F, \tag{5.2c}$$

$$\frac{\mathrm{d}I_F}{\mathrm{d}t} = \frac{z\beta}{N_M - J_M}I_M S_F - (\gamma_F + \frac{1}{\phi})I_F, \tag{5.2d}$$

$$\frac{\mathrm{d}J_M}{\mathrm{d}t} = j_M\frac{N_M}{\phi} - (\eta_M + \frac{1}{\phi})J_M, \tag{5.2e}$$

$$\frac{\mathrm{d}S_M}{\mathrm{d}t} = (1-j_M)\frac{N_M}{\phi} + \eta_M J_M - \frac{z\beta}{N_F - J_F}I_F S_M + \gamma_M I_M - \frac{1}{\phi}S_M, \tag{5.2f}$$

$$\frac{\mathrm{d}I_M}{\mathrm{d}t} = \frac{z\beta}{N_F - J_F}I_F S_M - (\gamma_M + \frac{1}{\phi})I_M. \tag{5.2g}$$

Assuming that one generation of the infection is measured as female infection to female infection we calculate R_0 as

$$R_0 = \frac{(z\beta)^2}{(\gamma_F + 1/\phi)(\gamma_M + 1/\phi)}. \tag{5.3}$$

For standard parameters from Table 3.2 ($z = 2$, $\beta = 0.6$, $\phi = 65$, $\gamma_F = \gamma_M = 1$), we estimate $R_0 \approx 1.4$.

5.2.1 Introducing Male Vaccination

Following analysis of the female-only vaccination strategy, we include male vaccination in the model by including a protected male class (P_M) that has the same parameters ($q(\alpha)$, α) as the female protected class. A proportion p_M of individuals enters the P_M class, with a corresponding female proportion, p_F, entering the female protected class.

5.3 Analysis

5.3.1 Solving the P_F and J_i Equations

We can solve the equations for P_F, J_F and J_M, as they can be uncoupled from the system. The solutions of these equations are

$$P_F = \frac{pN_F}{\phi(\alpha + 1/\phi)}(1 - e^{-(\alpha+1/\phi)t}), \tag{5.4}$$

which leads us to

$$J_F = \frac{B}{\eta_F + 1/\phi} - \frac{Ce^{-(\alpha+1/\phi)t}}{\eta_F - \alpha} + De^{-(\eta_F+1/\phi)t}, \qquad \eta \neq \alpha, \tag{5.5a}$$

$$J_F = \frac{B}{\eta_F + \frac{1}{\phi}} - Cte^{-(\eta_F+1/\phi)t} + \tilde{D}e^{-(\eta_F+1/\phi)t}, \qquad \eta = \alpha, \tag{5.5b}$$

where

$$B = [\frac{j_f(1-p)}{\phi} + \frac{q(\alpha)\alpha p}{\phi(\alpha + 1/\phi)}]N_F, \tag{5.6a}$$

$$C = \frac{q(\alpha)\alpha p}{\phi(\alpha + 1/\phi)}N_F, \tag{5.6b}$$

$$D = [\frac{J_F^0}{N_F} + \frac{q(\alpha)\alpha p}{\phi(\eta_F - \alpha)(\alpha + 1/\phi)} - \frac{j_F(1-p)(\alpha + 1/\phi) + q(\alpha)\alpha p}{\phi(\eta_F + 1/\phi)(\alpha + 1/\phi)}]N_F, \tag{5.6c}$$

$$\tilde{D} = J_F^0 - \frac{B}{\eta_F + 1/\phi}. \tag{5.6d}$$

The solution to J_M is

$$J_M = \frac{j_M N_M}{\phi(\eta_M + 1/\phi)} + J_M^0 e^{-(\eta_M+1/\phi)t}. \tag{5.7}$$

It is also possible to find the steady states for these classes; they are

$$P_F^* = \frac{pN_F}{\phi(\alpha + 1/\phi)},$$

$$J_F^* = \frac{(1-p)(\alpha + 1/\phi)j_F N_F + q(\alpha)\alpha p N_F}{\phi(\eta_F + 1/\phi)(\alpha + 1/\phi)},$$

and

$$J_M^* = \frac{j_M N_M}{\phi(\eta_M + 1/\phi)}.$$

5.3.2 Steady States and their Stability

We can find the steady states of the system; those for P_F and J_i are given above and the remaining classes at steady state are

$I_F^* = 0$ and $I_M^* = 0$ or

$$I_F^* = (z\beta)\frac{((1-\frac{1}{R_0})(N_F - J_F^*) - P_F^*)}{(z\beta + \gamma_F + 1/\phi)},$$

and

$$I_M^* = \frac{(z\beta)(N_M - J_M^*)((1-\frac{1}{R_0})(N_F - J_F^*) - P_F^*)}{z\beta(N_F - P_F^* - J_F^*) + (\gamma_M + 1/\phi)(N_F - J_F^*)}.$$

Substituting all other steady state values into the equations for N_i gives the steady state values of S_i ($S_F^* = N_F^* - P_F^* - J_F^* - I_F^*$, $S_M^* = N_M^* - J_M^* - I_M^*$).

Analysis of the full model system (5.2) can be reduced to explore the behaviours of an equivalent 2-D system in the following way. The governing equations for P_F, J_F and J_M are uncoupled from the remainder of the system and hence stability of their steady states can also be determined separately from the full system. Since we are assuming a constant population size for each of the males and females, the dimension of the infection system (S_F, I_F, S_M, I_M) can further be reduced to consider the two dimensional system for (I_F, I_M):

$$\frac{\mathrm{d}I_F}{\mathrm{d}t} = \frac{z\beta}{N_M - J_M} I_M(N_F - P_F - J_F - I_F) - (\gamma_F + \frac{1}{\phi})I_F, \tag{5.8a}$$

$$\frac{\mathrm{d}I_M}{\mathrm{d}t} = \frac{z\beta}{N_F - J_F} I_F(N_M - J_M - I_M) - (\gamma_M + \frac{1}{\phi})I_M, \tag{5.8b}$$

where $J_F(t)$, $P_F(t)$ and $J_M(t)$ are determined from the full system; see the previous subsection. Behaviour of the full system can then be inferred from the behaviour of the 2-D system. We calculate the stability of the disease-free steady state ($I_F^* = I_M^* = 0$) using the Jacobian of (5.8) evaluated at that point. This gives

$$B = \begin{pmatrix} -(\gamma_F + \frac{1}{\phi}) & \frac{z\beta(N_F - P_F^* - J_F^*)}{N_M - J_M^*} \\ \frac{z\beta(N_M - J_M^*)}{N_F - J_F^*} & -(\gamma_M + \frac{1}{\phi}) \end{pmatrix}. \tag{5.9}$$

Stability of this steady state requires that $\mathrm{tr}(J) < 0$ and $\det(J) > 0$. Since $\mathrm{tr}(J) < 0$ for all parameter combinations, stability of the disease-free steady state requires that

$$(\gamma_F + \frac{1}{\phi})(\gamma_M + \frac{1}{\phi}) > \frac{(z\beta)^2(N_F - P_F^* - J_F^*)}{N_F - J_F^*}, \tag{5.10}$$

i.e.

$$\frac{R_0(N_F - P_F^* - J_F^*)}{N_F - J_F^*} < 1. \tag{5.11}$$

For $\frac{R_0(N_F-P_F^*-J_F^*)}{N_F-J_F^*} < 1$ the disease-free steady state is stable, and is the only steady state of the system. For $\frac{R_0(N_F-P_F^*-J_F^*)}{N_F-J_F^*} > 1$, the disease-present steady state exists and the disease-free steady state is unstable (this is an example of a transcritical bifurcation).

5.3.3 "Effective" R_0, R_0^e

Using (5.11), we see that $R_0^e = \frac{R_0(N_F-P_F^*-J_F^*)}{N_F-J_F^*} = R_0(1 - f(p))$ where

$$f(p) = \frac{p(\eta_F + 1/\phi)}{\phi(\eta_F + 1/\phi)(\alpha + 1/\phi) - ((1-p)(\alpha + 1/\phi)j_F + q(\alpha)\alpha p)}. \tag{5.12}$$

Eradication of infection in the population is only possible if $R_0^e < 1$, which corresponds to

$$f(p) > 1 - \frac{1}{R_0}. \tag{5.13}$$

With the introduction of male vaccination, R_0^e is modified to
$R_0^e = R_0(1 - f_F(p))(1 - f_M(p))$, where

$$f_i(p) = \frac{p(\eta_i + 1/\phi)}{\phi(\eta_i + 1/\phi)(\alpha + 1/\phi) - ((1-p)(\alpha + 1/\phi)j_i + q(\alpha)\alpha p)}. \tag{5.14}$$

Initially we specify all gender specific parameters to be the same, which means that $R_0^e = R_0(1 - f(p))^2$, and then infection can only be eradicated for the condition

$$f(p) > 1 - \frac{1}{\sqrt{R_0}}. \tag{5.15}$$

We use (5.12)-(5.15) to explore the interplay between key behavioural parameters j_i and η_i, and vaccination parameters p and α in predicting conditions under which HPV could be eradicated by an appropriate vaccination strategy. The dependence of $f(p)$ on these parameters in the case of female-only vaccination is shown in Figures 5-2a, 5-2c and 5-2e, from which we see that $f(p)$ is an increasing function of p but a decreasing function of both α and η_F, with variation in α causing the greatest variation in $f(p)$. According to (5.13) and (5.15), eradication of infection can only occur if $f(p)$ is sufficiently large - we see from Figure 5-2 that this will only happen if either p is sufficiently large or if η_F or α is sufficiently small, with small α giving the largest change in $f(p)$.

5.3.4 Vaccination in a Population already Sexually Active

Setting $q(\alpha) = j_i = 0$, we consider a vaccination strategy aimed at a population of sexually active individuals. This is analogous to previous work presented in [68] and gives the following results:

- For female-only vaccination

$$R_0^e = R_0(1 - \frac{p}{\phi(\alpha + 1/\phi)}). \tag{5.16}$$

- With female and male vaccination

$$R_0^e = R_0(1 - \frac{p}{\phi(\alpha + 1/\phi)})^2. \tag{5.17}$$

In both cases, as α decreases the period of vaccine efficacy increases and the proportion of the population that should be vaccinated to eradicate HPV is reduced; this reduction is more pronounced when both males and females are vaccinated. For example, the value of p required when α is essentially lifelong ($\alpha = 1/\phi$) is less than half of that required for p when the vaccine lasts for 20 years (all other parameters being equal) for both female-only vaccination and for vaccination of both sexes, although in the case of vaccination of both sexes, R_0^e can be driven below 1 for a lower p value.

5.3.5 Female-only Vaccination

Figure 5-3 shows how R_0^e, for female-only vaccination as given by (5.16), varies with the key model parameters. Using parameters from Table 3.2 we see that changes to η_F are not able to drive infection from the population for any level of vaccination. By contrast, provided that the vaccination is sufficiently long-lasting (α small) then if p is large enough infection may be eradicated. For example, a vaccine lasting for at least 20 years ($\alpha = 0.05$) in a population averaging 2 partners per year ($z = 2$), with coverage of at least 70% of the female population ($p \geq 0.7$), can drive $R_0^e < 1$. Whilst changes in η_F do not have a great impact on R_0^e, another behavioural parameter, z, does. In particular, a reduction of z by less than 25% (z reduced from 2 to $z = 1.6$) results in $R_0^e < 1$ for a range of parameters.

5.3.6 Female and Male Vaccination

In Figure 5-2 we compare conditions (5.13) and (5.15), from which we see that the addition of male vaccination makes eradication of infection possible for a wider range

of parameter values. Where eradication is not possible, male vaccination allows the system to have a lower R_0^e.

5.3.7 Critical Values

Corresponding to $R_0^e = 1$ for the case with female-only vaccination, we can derive critical values for η_F and α;

$$\eta_F^{crit} = \frac{(1-\frac{1}{R_0})((1-p)(\alpha+1/\phi)j_F + q(\alpha)\alpha p)}{\phi(\alpha+1/\phi)(1-\frac{1}{R_0}) - p} - \frac{1}{\phi}.$$

As $q = q(\alpha)$, we can analytically define α^{crit} in terms of $q(\alpha)$ as

$$\alpha^{crit} = \frac{p(\eta_F + 1/\phi) - (1-\frac{1}{R_0})(\eta_F + \frac{1}{\phi} - \frac{(1-p)j_F}{\phi})}{(1-\frac{1}{R_0})(\phi(\eta_F+1/\phi) - (1-p)j_F) - q(\alpha^{crit})p}.$$

With $q(\alpha) = \frac{0.616\alpha+0.05}{1+\alpha}$, we obtain a quadratic for α^{crit};

$$\begin{aligned}(\phi(\eta_F + \frac{1}{\phi}) - (1-p)j_F - \frac{0.616p}{(1-1/R_0)})(\alpha^{crit})^2 \\ + ((\phi(\eta_F + \frac{1}{\phi}) - (1-p)j_F)(1+\frac{1}{\phi}) - \frac{(p(\eta_F + \frac{1}{\phi} + 0.05))}{(1-\frac{1}{R_0})})\alpha^{crit} \\ - (\frac{p(\eta_F + \frac{1}{\phi})}{(1-\frac{1}{R_0})} - (\eta_F + \frac{1-(1-p)j_F}{\phi})) = 0. \quad (5.18)\end{aligned}$$

The solutions of (5.18) are

$$\alpha^{crit} = \frac{-k \pm \sqrt{k^2 + 4(\phi(\eta_F + \frac{1}{\phi}) - (1-p)j_F - \frac{0.616p}{(1-1/R_0)})(\frac{p(\eta_F+\frac{1}{\phi})}{(1-\frac{1}{R_0})} - (\eta_F + \frac{1-(1-p)j_F}{\phi}))}}{2(\phi(\eta_F + \frac{1}{\phi}) - (1-p)j_F - \frac{0.616p}{(1-1/R_0)})}. \quad (5.19)$$

where $k = ((\phi(\eta_F + \frac{1}{\phi}) - (1-p)j_F)(1+\frac{1}{\phi}) - \frac{(p(\eta_F+\frac{1}{\phi}+0.05))}{(1-\frac{1}{R_0})}))$. We now let $m = (\phi(\eta_F + \frac{1}{\phi}) - (1-p)j_F - \frac{0.616p}{(1-1/R_0)})$ and $n = (\frac{p(\eta_F+\frac{1}{\phi})}{(1-\frac{1}{R_0})} - (\eta_F + \frac{1-(1-p)j_F}{\phi}))$. If $m > 0$, $n > 0$ and $k < 0$, either solution given in (5.19) is positive. If $\alpha^{crit} < 0$, it means that the disease could be eradicated regardless of the duration of protection offered by the vaccine. For our standard parameter set, $m > 0$, $k > 0$ and $n < 0$, giving $\alpha^{crit} \approx 0.023$.

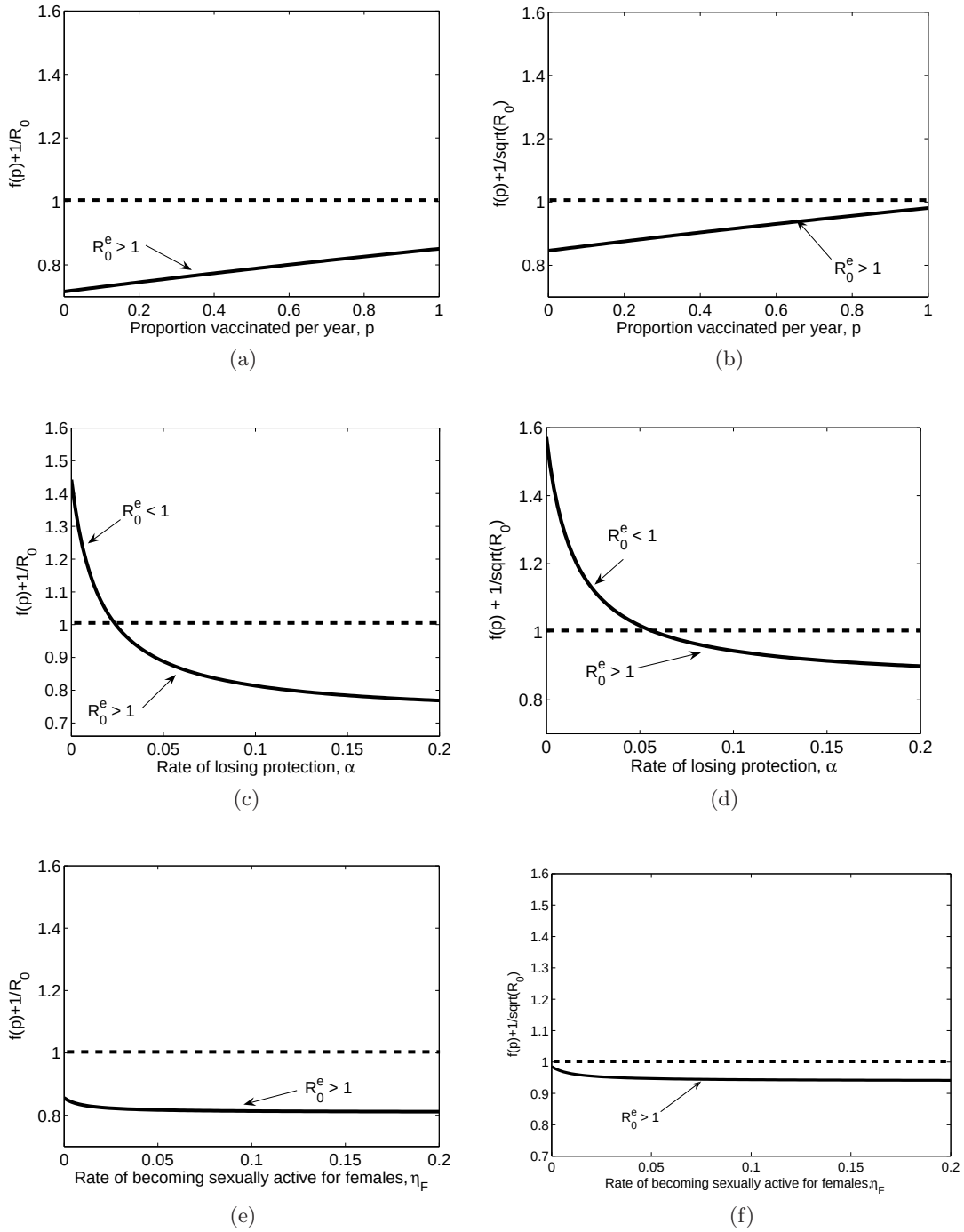
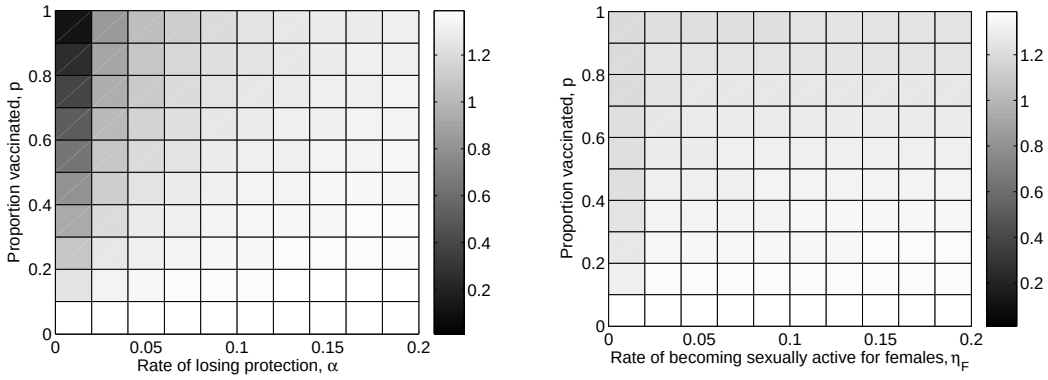


Figure 5-2: Graphs showing how varying different parameters affects the point at which $R_0^e = 1$, for the cases both with and without male vaccination. Figures 5-2a, 5-2c and 5-2e show the case when there is no male vaccination. The other graphs represent the situation with male vaccination. All parameters used are given as estimates in Table 3.2.



(a) (b)

Figure 5-3: Two graphs showing the effect on R_0^e of varying two parameters. Figure 5-3a shows the change in R_0^e against α and p, whereas 5-3b shows R_0^e against η_F and p. All other parameters are standard, taken from Table 3.2.

We can do the same to find a critical value for p, p^{crit}. This gives us

$$p^{crit} = \frac{[\phi(\alpha + 1/\phi)(1 - 1/R_0)(\eta_F + (1 - j_F)/\phi)]}{(\eta_F + 1/\phi + (1 - 1/R_0)(\alpha(q(\alpha) - j_F) - j_F/\phi))}. \tag{5.20}$$

For $R_0^e < 1$, we require $p > p^{crit}$. From the equation (5.20) we can see that, for $R_0 < 1$, $p^{crit} < 0$ - i.e. that there is no minimum level of vaccination required to eradicate the disease. When $R_0 > 1$, $p^{crit} > 0$ provided $(\eta_F + 1/\phi)(\frac{R_0}{R_0 - 1}) > (\alpha(j_F - q(\alpha)) + j_F/\phi)$.

5.4 Numerical Solutions

We numerically solve the model both with and without male vaccination. Figure 5-4 shows infection prevalence for females and males corresponding to the R_0^e values shown in Figure 5-3, for the case of female-only vaccination. This highlights the heterogeneity in infection prevalence between the two sexes as a result of a female-only vaccination strategy. The initial conditions used are $P_i(0) = 0$, $J_i(0) = 25000$, $S_i(0) = 90750$ and $I_i(0) = 9250$, which are estimated using available data.

Figure 5-5 is analogous to Figure 5-4 and highlights two changes which arise with the inclusion of male vaccination:

1. Infection prevalence in both sexes is the same when varying α and p since the vaccination is the same for both sexes.

2. There is a wider range of parameter values for which infection can be removed from the population.

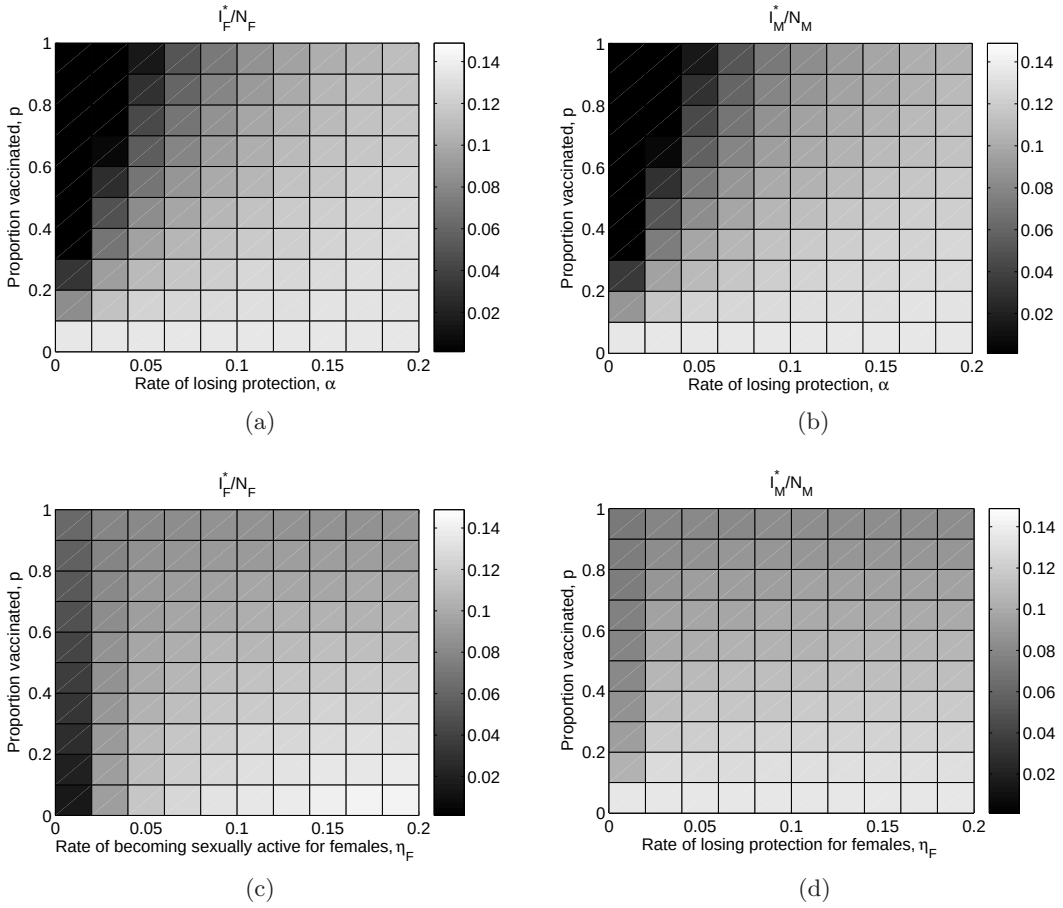


Figure 5-4: Four graphs showing the effect on the female and male infected steady states as different parameters are varied. Figures 5-4a and 5-4b show the female and male infected steady states as α and p are varied; 5-4c and 5-4d show the steady states as η_F and p vary. All parameters come from the estimated values given in Table 3.2.

To directly compare the two vaccination strategies (female-only versus both sexes), we compare values of $f(p)$ required to achieve $R_0^e = 1$ in (5.13) and (5.15) respectively. The proportional reduction in $f(p)$ when male vaccination is added to female-only vaccination is given as

$$\Lambda = \frac{f(p)|_{female\text{-}only} - f(p)|_{female\ and\ male}}{f(p)|_{female\text{-}only}}, \tag{5.21}$$

i.e.

$$\Lambda = \frac{\sqrt{R_0} - 1}{R_0 - 1}. \tag{5.22}$$

With $R_0 \approx 1.4$, male vaccination leads to around 45% reduction in the proportion that should be vaccinated, although the population is now doubled to $N_F + N_M$. This means that a greater number of individuals must be vaccinated than under female-only vaccination. In fact, (5.22) shows that the percentage reduction will only be greater than 50% when $R_0 < 1$.

Figure 5-6 shows the time profiles for each compartment of the population for the model with and without male vaccination, and surface plots for the number of individuals in the protected and infected classes as the proportion of females vaccinated (p_F) and males vaccinated (p_M) varies. The class profiles show that male vaccination, when implemented at the same level as female vaccination, does not alter the path of the profiles. The surface plots suggest that there is a symmetry between p_F and p_M, although the exact values show that there is a slight decrease in the total number of infecteds when male vaccination is included, compared to female-only vaccination. It does show that it is possible to halve the value of p so that the same total number of individuals are vaccinated and not see an increase in infection prevalence.

5.5 Adding Natural Immunity

As a comparison to the SIS model presented thus far, we now introduce a recovered class to consider an $SIRS$ model as shown in Fig 5-7. Both SIS and SIR models have previously been considered in relation to this topic [33, 39, 57] and as such it is of interest to consider the different results produced when a (naturally) immune class is introduced. As we can see from the schematic, the recovery can be permanent or temporary, depending on the value of the parameter ϵ_i, and the proportion of individuals that develop natural immunity can be varied by varying σ_i. On studying this system, the values of P_F^*, J_F^* and J_M^* are unchanged from the system without natural immunity. We can once again solve for S_i^* by using $S_F^* = N_F - P_F^* - J_F^* - I_F^* - R_F^*$

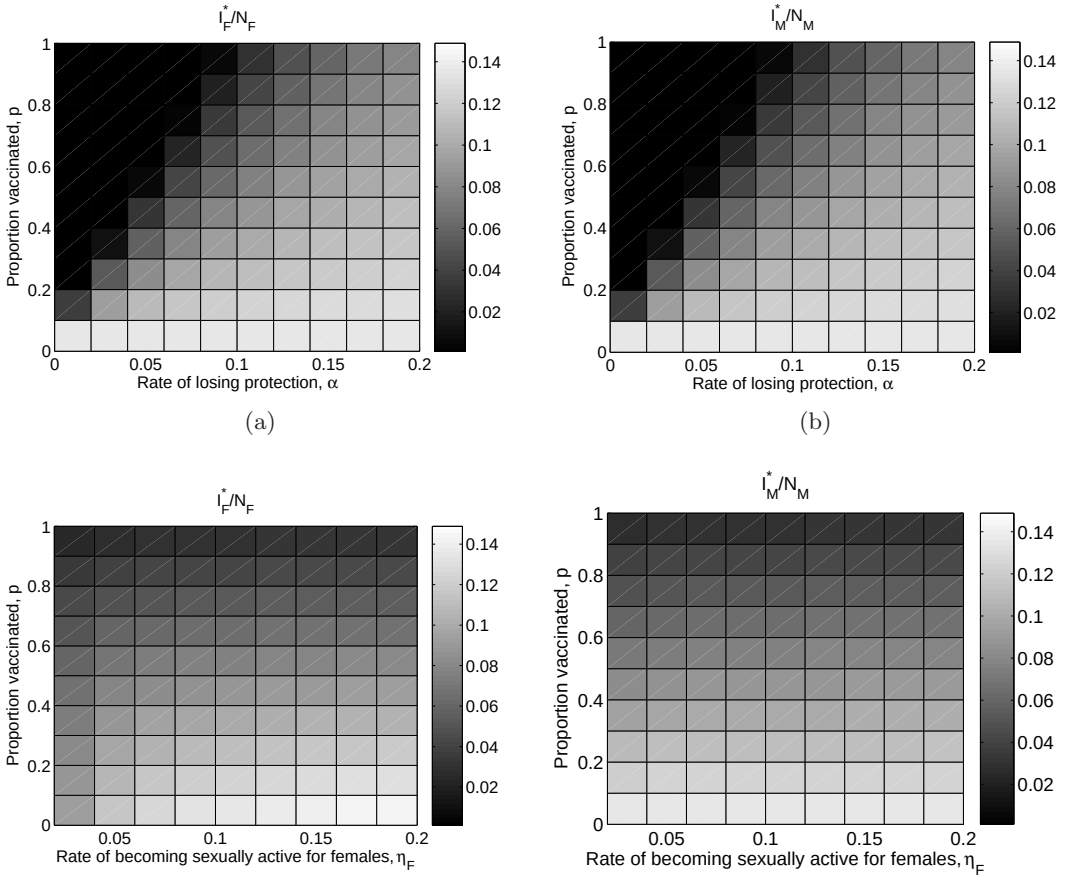


Figure 5-5: Four graphs showing the effect on the female and male infected steady states as different parameters are varied for vaccination of both sexes. Figures 5-5a and 5-5b show the female and male infected steady states as α and p are varied; 5-5c and 5-5d show the steady states as η_F and p vary. All parameters come from the estimated values given in Table 3.2.

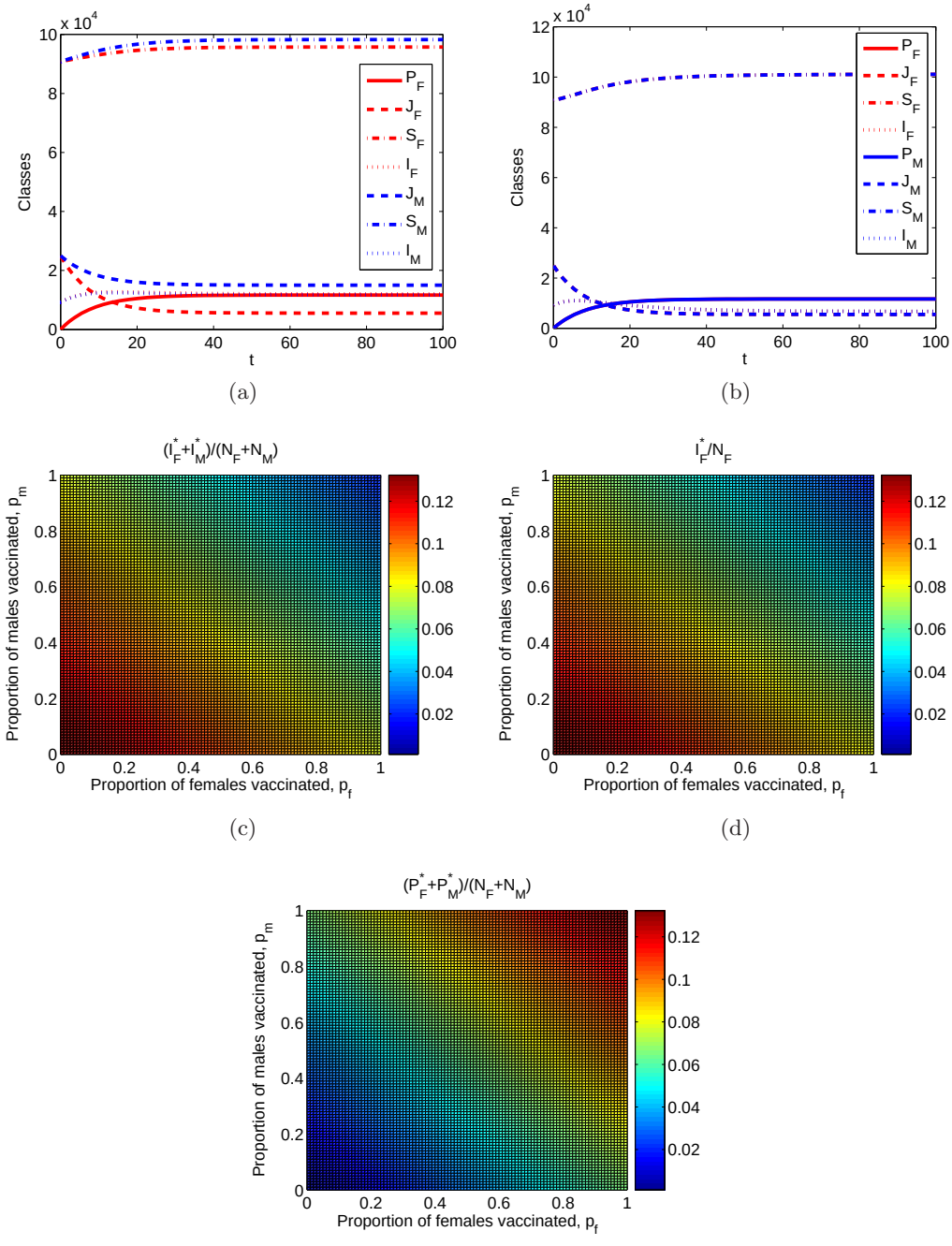


Figure 5-6: Graphs showing the class profiles for the model without male vaccination (Figure 5-6a) and the model with male vaccination (Figure 5-6b; the female class profiles lie under the the male ones). The second set of figures (Figures 5-6c, 5-6d and 5-6e) show the total numbers of individuals in each type of class (Infected classes, Infected female class, Protected classes) for the model as the proportion of both female vaccinated (p_F) and male vaccinated (p_M) varies. The parameter values are all taken from the standard set as seen in Table 3.2.

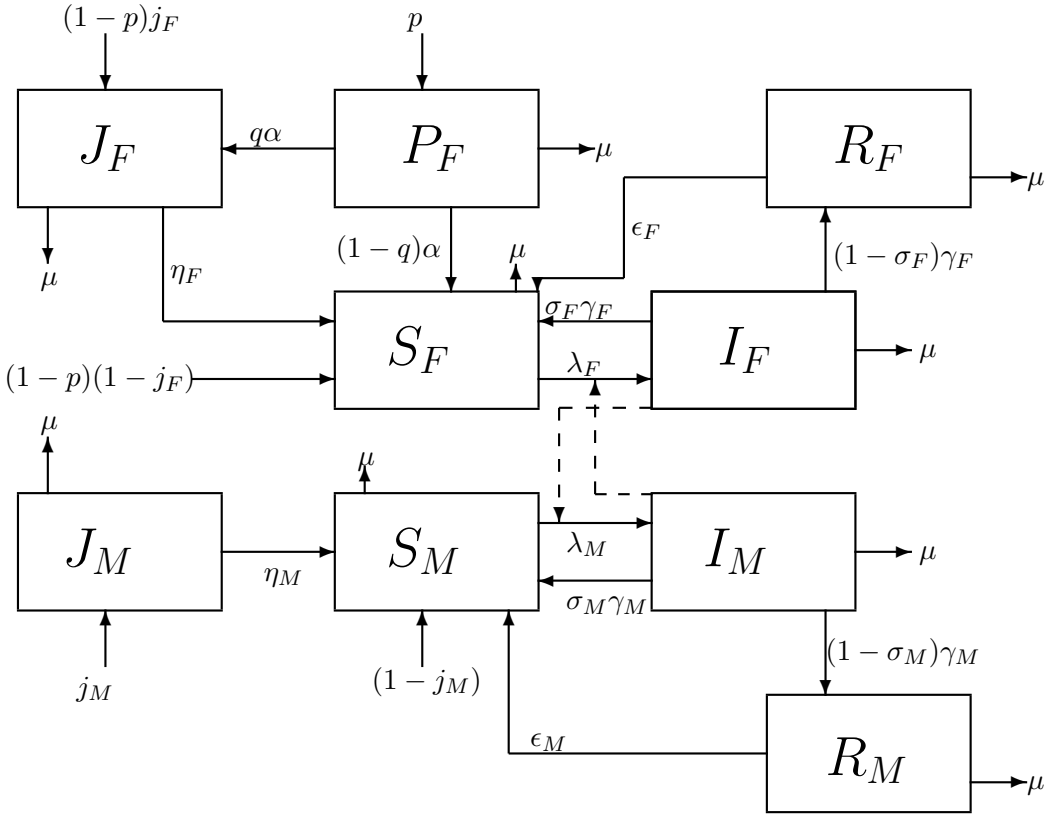


Figure 5-7: A schematic of the ODE model with genders and natural immunity.

and $S_M^* = N_M - J_M^* - I_M^* - R_M^*$, where the equations for the R_i classes are

$$\frac{\mathrm{d}R_i}{\mathrm{d}t} = (1-\sigma_i)\gamma_i I_i - (\epsilon_i + \mu)R_i, \tag{5.23}$$

giving

$$R_i^* = \frac{(1-\sigma_i)\gamma_i}{\epsilon_i + \mu} I_i^*. \tag{5.24}$$

The disease-present steady states for I_i^* are affected by the existence of the R_i classes, and become

$$I_F^* = (z\beta)\frac{((1-\frac{1}{R_0})(N_F - J_F^*) - P_F^*)}{(z\beta(1+\frac{(1-\sigma_F)\gamma_F}{\epsilon_F+1/\phi}) + (\gamma_F + 1/\phi)(1+\frac{(1-\sigma_M)\gamma_M}{\epsilon_M+1/\phi}))},$$

and

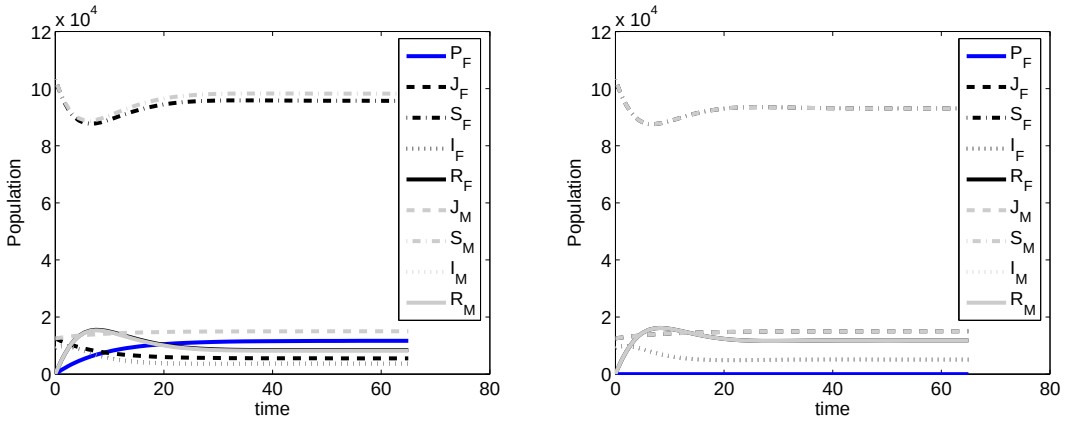
$$I_M^* = \frac{(z\beta)(N_M - J_M^*)((1-\frac{1}{R_0})(N_F - J_F^*) - P_F^*)}{z\beta(1+\frac{(1-\sigma_M)\gamma_M}{\epsilon_M+1/\phi})(N_F - P_F^* - J_F^*) + (\gamma_M + 1/\phi)(1+\frac{(1-\sigma_F)\gamma_F}{\epsilon_F+1/\phi})(N_F - J_F^*)}.$$

The denominators are clearly positive, and so for these steady states to exist, we require the numerators to be positive. These are exactly the same as those given in the system without natural immunity. Equally, steady state analysis is the same with or without natural immunity, so the work shown on R_0^e for the SIS model above is also applicable here.

Figure 5-8 shows a plot of the class profiles over time when natural immunity is included in the model. Comparing it to Figure 5-6a shows that the introduction of natural immunity does not qualitatively affect the outcome; infection is still present in the model both with and without protection.

5.6 Conclusions

The results of this model show that, under certain circumstances, it is possible to force R_0^e under 1, and thus it may be possible to eradicate HPV from the population. We assessed the effect that different behavioural and vaccination parameters have on the value of R_0^e. Figures 5-2a, 5-2c and 5-2e show that by increasing the proportion vaccinated, the value of R_0^e will decrease. We see the opposite effect with α and η_F, as an increase in either of these parameters will cause R_0^e to increase. These are all as we would expect, and we note that there is close to a linear relationship between p and $f(p)$, but a nonlinear relationship exists between both α and $f(p)$ and between η_F and $f(p)$. We also see that changing the value of α has the greatest effect on $f(p)$,



(a) (b)

Figure 5-8: A graph of the class profiles over time when natural immunity is included in the model. In the Figure 5-8a, vaccination is included; in 5-8b, there is no vaccination present and the female classes lie underneath the male classes. All parameters and initial conditions are as before (see Table 3.2); $\sigma_i = 0.5$, $\epsilon_i = 0.2$.

suggesting that the duration of vaccine protection will have an important effect on the final outcome.

Figure 5-2 shows how varying certain parameters can affect whether $R_0^e < 1$ or not, and we find that only for a long duration of protection is it possible to force $R_0^e < 1$. However, the duration of protection needed for this to happen is decreased when male vaccination is included, suggesting that male vaccination may come into play if the vaccination is shown to last less than 40 years.

The impact of α is confirmed in Figure 5-3, where we see plots of R_0^e against different parameters. For a value of $\alpha = 0.1$, varying η_F and p cannot force R_0^e under 1, but for a value of $\eta_F = 0.1$, varying α and p shows that, for $\alpha < 0.04$ and $p > 0.7$, it is possible to push $R_0^e < 1$ (for $p = 0.7$, $\alpha = 0.023$ is the critical point for $R_0^e = 1$).

Figure 5-4 shows how the values of different parameters affects the infected steady states directly. This again supports the hypothesis that α has a much greater impact than η_F, especially at higher values of p. Figures 5-4a and 5-4b show that, for a low value of α, it is possible to reach the disease-free steady state (in both genders), but that the disease-free steady state cannot be reached for $\alpha = 0.1$ and varying η_F and p.

Figure 5-5 shows plots of infection prevalence (as in Figure 5-4), but for a model containing both male and female vaccination. As expected, including vaccination on both sexes increases the range of values of α and η_F for which prevalence is very low, although this occurs for a wider range of values when varying α and p than when varying η_F and p - which matches the results gained from the case of female-only vaccination.

We also saw that the inclusion of male vaccination (at the same rate as for females) led to a decrease of 45% in the percentage of individuals that needed to be vaccinated. However, as these individuals came from both the male and female classes, this actually leads to an increase in the total number of individuals that need to be vaccinated. We found that it would only be possible to vaccinate fewer individuals when $R_0 < 1$ and vaccination may not be appropriate in this case anyway.

Figure 5-6 shows the benefit of including male vaccination. The values found when including male vaccination indicate that vaccinating the same number of individuals (both males and females) as would be vaccinated in the female-only vaccination strategy leads to a slight decrease in the total prevalence of infection at steady state compared to female-only vaccination. This is positive in itself, but holds further benefits if HPV becomes recognised as a significant factor in other genital cancers.

Figure 5-8 shows the class profiles when the SIS model introduced at the start of the Chapter is adapted to an $SIRS$ format. The $SIRS$ model (with the same set of parameter values and initial conditions as for the SIS model) indicates that, with or without a protected class, the results are qualitatively similar to the results from the SIS model. Indeed, varying the σ_i and ϵ_i values suggested that the disease would only be eradicated in the population when almost all ($\sigma_i \approx 0$) individuals became (permanently - $\epsilon_i \approx 0$) naturally immune.

These results show the importance of considering a range of different factors when assessing the potential success of the vaccine. We see that the most important vaccination parameter of those we considered was α. From the behavioural parameters considered, it is clear that the value of z will also have an important effect, as we find it is possible to force $R_0^e < 1$ by varying z, where other behavioural parameters (e.g. the rate at which individuals become sexually active) cannot.

The inclusion of a non-sexually active class is a key difference between the work presented here and most previous work, although [36] do introduce this idea for females. Coupled with the inclusion of waning immunity, having this class allows us to explicitly consider the effect of vaccination for a sexually transmitted infection in a group that is (largely) not yet sexually active. We also consider male vaccination, and the effect this has, specifically the impact of male vaccination on values such as R_0^e.

The importance of interplay between vaccination, epidemiological and behavioural parameters is clearly demonstrated here. Of these, epidemiological parameters are essentially fixed but vaccination parameters may be adjusted via public health strategy (p) and further pharmaceutical developments (α). Modifying behavioural parameters (j_i, η_i, z) to assist the effectiveness of the vaccination programme is a more challenging problem, which might only be addressed by educational programmes. Whether the

significance of altering behaviours can be made clear through such a programme remains to be seen.

Chapter 6

The PDE model

6.1 Introduction

Sexually transmitted infections often lend themselves to age-structured models for several reasons. Sexual mixing occurs mainly between individuals of a similar age [43, 59]; transmission probabilities can vary dependent on age [31] and sexual behaviour often changes with age [3]. In our case, vaccination is targeted at a specific age group [2]. All of these factors indicate that an age-structured model may give us more accurate results.

The aim of this Chapter is to build a model that is both age- and time-dependent. We first consider an age-dependent ODE, then go on to study an age- and time-dependent PDE, generating numerical solutions and comparing the results to both the age-dependent ODE and the time-dependent model presented in Chapter 5.

We consider the model discussed in previous chapters as a system of PDE equations, dependent on age (a) and time (t). The inclusion of age as well as time allows us to include age-dependence in key behavioural parameters. A discussion of these parameters, and the age-dependent functions used, is given in Chapter 3.

6.2 ODE Model

We commence this Chapter by considering the age-dependent ODE model that is comparable to the time-dependent ODE models shown in Chapters 4 and 5. The key difference to the time-dependent ODE models is that our parameters can be represented by age-dependent functions (given in Chapter 3); for completeness we also consider the model with constant parameters. The schematic from which the ODE model is derived is shown in Figure 6-1, and we consider the classes as only age-dependent.

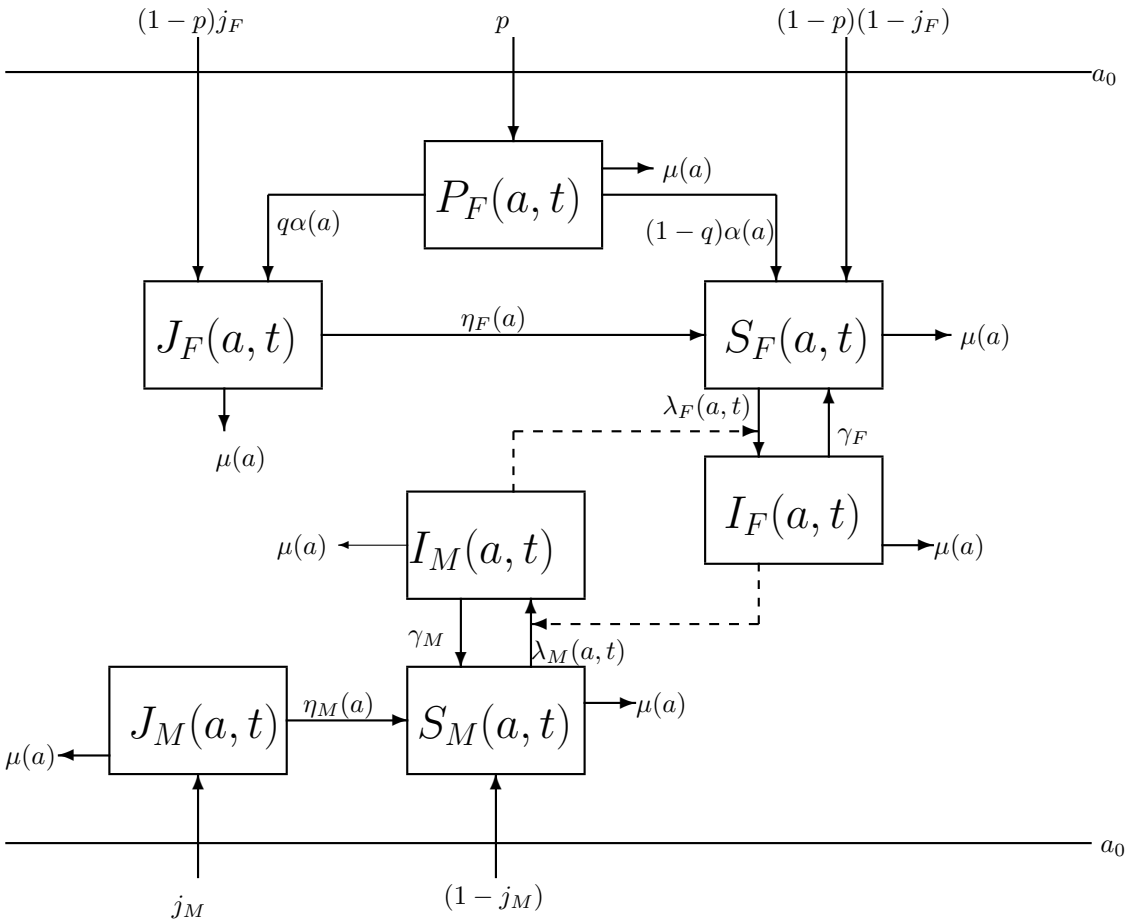


Figure 6-1: A schematic of the system.

From the schematic and considering only the temporally stable case, the ODE model is

$$\frac{\mathrm{d}P_F}{\mathrm{d}a} = -(\alpha(a) + \mu_F(a))P_F, \tag{6.1a}$$
$$\frac{\mathrm{d}J_F}{\mathrm{d}a} = -(\eta_F(a) + \mu_F(a))J_F + q(\alpha)\alpha(a)P_F, \tag{6.1b}$$
$$\frac{\mathrm{d}S_F}{\mathrm{d}a} = -(\lambda_F(a) + \mu_F(a))S_F + (1 - q(\alpha))\alpha(a)P_F + \eta_F(a)J_F + \gamma_F I_F, \tag{6.1c}$$
$$\frac{\mathrm{d}I_F}{\mathrm{d}a} = -(\gamma_F + \mu_F(a))I_F + \lambda_F(a)S_F, \tag{6.1d}$$
$$\frac{\mathrm{d}J_M}{\mathrm{d}a} = -(\eta_M(a) + \mu_M(a))J_M, \tag{6.1e}$$
$$\frac{\mathrm{d}S_M}{\mathrm{d}a} = -(\lambda_M(a) + \mu_M(a))S_M + \eta_M(a)J_M + \gamma_M I_M, \tag{6.1f}$$
$$\frac{\mathrm{d}I_M}{\mathrm{d}a} = -(\gamma_M + \mu_M(a))I_M + \lambda_M(a)S_M, \tag{6.1g}$$
$$\frac{\mathrm{d}N_F}{\mathrm{d}a} = -\mu_F(a)N_F, \tag{6.1h}$$
$$\frac{\mathrm{d}N_M}{\mathrm{d}a} = -\mu_M(a)N_M. \tag{6.1i}$$

All parameters are as discussed in Chapter 3. In the work that follows, we use two different definitions for λ_i $(i = F, M)$. In the first case we assume homogeneous mixing, and so use a version of λ_i, λ_i^l, which is defined as

$$\lambda_i^l(a) = z_i(a)\beta \int_{a_0}^{a_{max}} \frac{I_k(a')}{N_k(a') - J_k(a')} \quad \mathrm{d}a', \tag{6.2}$$

$i, k = F, M$, $i \neq k$, $z_i(a)$ and β are as defined in Chapter 3 [31].

However, for an age-dependent model, this does not take into account any heterogeneity of relationships occurring between individuals of different ages. To allow for this, we assume heterogeneous mixing; the definition of this λ_i, λ_i^h, is

$$\lambda_i^h(a) = z_i(a) \int_{a_0}^{a_{max}} \beta(a, a') \frac{I_k(a')}{N_k(a') - J_k(a')} \quad \mathrm{d}a', \tag{6.3}$$

[31]. As described in Chapter 3, we set $\beta(a, a') = \beta A$, where β is the constant probability of transmission and A is a contact matrix, giving the probability of contact between individuals of age a and a'.

To complete the model, we set the boundary conditions at age a_0. These were estimated as $P_F(a_0) = 0.7N_F(a_0)$, $J_F(a_0) = 0.225N_F(a_0)$, $S_F(a_0) = 0.025N_F(a_0)$, $I_F(a_0) = 0.05N_F(a_0)$, $J_M(a_0) = 0.855N_M(a_0)$, $S_M(a_0) = 0.095N_M(a, 0)$ and $I_M(a_0) = 0.05N_M(a_0)$.

6.3 Solving the Equations

We can solve (6.1a), (6.1b), (6.1e), (6.1h) and (6.1i) analytically, giving the solutions

$$P_F(a) = P_F(a_0)e^{-\int_{a_0}^{a}(\alpha(s)+\mu_F(s))\ \mathrm{d}s}, \tag{6.4}$$

$$J_F(a) = J_F(a_0) + P_F(a_0)e^{-\int_{a_0}^{a}(\eta_F(s)+\mu_F(s))\ \mathrm{d}s}\int_{a_0}^{a}\alpha(w)q(\alpha)e^{-\int_{a_0}^{w}(\eta_F(s)-\alpha(s))\ \mathrm{d}s}\ \mathrm{d}w, \tag{6.5}$$

$$J_M(a) = J_M(a_0)e^{-\int_{a_0}^{a}(\eta_M(s)+\mu_M(s))\ \mathrm{d}s}, \tag{6.6}$$

and

$$N_i(a) = N_i(a_0)e^{-\int_{a_0}^{a}\mu(s)\ \mathrm{d}s}, \tag{6.7}$$

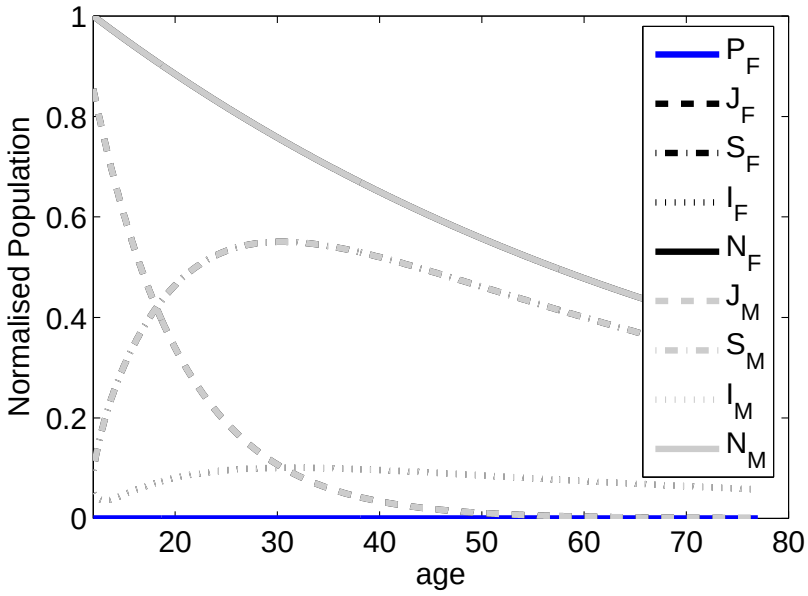
with $i = F, M$.

6.4 Numerical Solutions

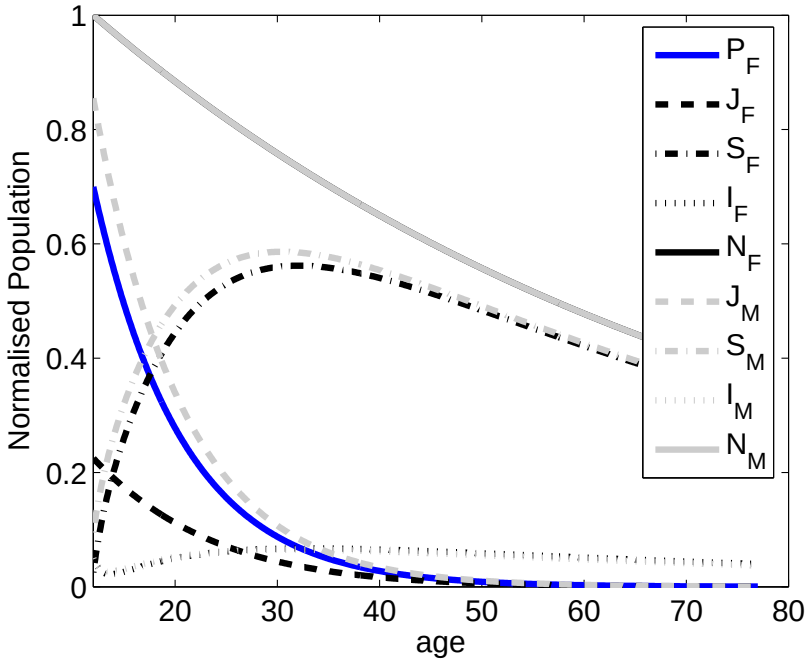
From this model, we considered four different situations. We used either the 'homogeneous mixing' form of λ_i (6.2) or the more complicated form (6.3), and in each case we used either constant or age-dependent parameters. The sections that follow consider each of these cases and show the different results. We use a fourth order Runge-Kutta numerical scheme to solve the equations. To find the values of λ_i, we use an iterative method. We solve the model equations for the initial conditions and calculate the value of λ_i. We repeat this, updating the values of λ_i after each iteration, until each of the model equations and λ_i values converge to a solution. The Matlab code is given in Appendix B.

6.4.1 Model with Constant Parameters, λ_i^l

This takes (6.1) and uses the constant parameter values given in Table 3.2 and (6.2) (λ_i^l) as described above. Using Matlab to solve this numerically gives the class profiles as shown in Figure 6-2, both with and without protection. In this case, we see that infection persists in the model when a protected class exists, but that the proportion of infected individuals is decreased by the presence of a vaccine.



(a)



(b)

Figure 6-2: A graph showing all classes of the model with constant parameter values and the λ_i^l. The parameter values and initial conditions are as described in Table 3.2 and in this Chapter, with $\gamma_i = 1$. Figure 6-2a shows the system when there is no protected class (here the female classes lie underneath the male classes) and Figure 6-2b shows the system with a protected class and an average duration of immunity from vaccination of 10 years.

6.4.2 Model with Age-dependent Parameters, λ_i^l

This model uses the age-dependent set of parameters described in Chapter 3, but keeps (6.2) as the force of infection. We also reduce γ_i to $\gamma_i = 0.8$ as the introduction of age-dependent parameters reduces infection to very low levels. The numerical solution is given in Figure 6-3. As in the previous subsection, we can see that infection persists even when vaccination is included. We find that the peak of the proportion of infected individuals is halved when vaccination is introduced. In contrast to Figure 6-2, the population remains very close to 1 until $a \approx 40$, when it starts to decrease slowly. The survivorship curve shown in Figure 6-2 is more appropriate for 'Type II' survival [31]. Survival in Western countries tends to follow a 'Type I' survivorship curve, which is approximated in Figure 6-3.

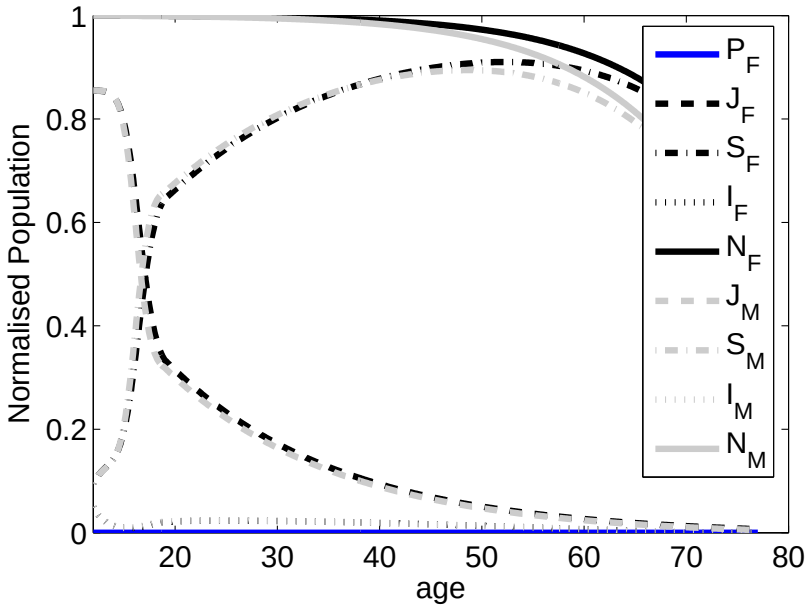
6.4.3 Model with Constant Parameters, λ_i^h

We next move to the case of constant parameters and λ_i^h, given in (6.3). The class profiles are shown in Figure 6-4, again both with and without a protected class. Once more we see that infection is present in both situations, although there is a higher proportion of infected individuals when there is no protection. We also see that when protection is included, the 'take-off' of infection is delayed and occurs only when the protected class is very small. The biggest contrast between this case and Figure 6-3 is the survival curve - here, as in Figure 6-2, the shape of the survival curve is more suited to 'Type II' survival [31].

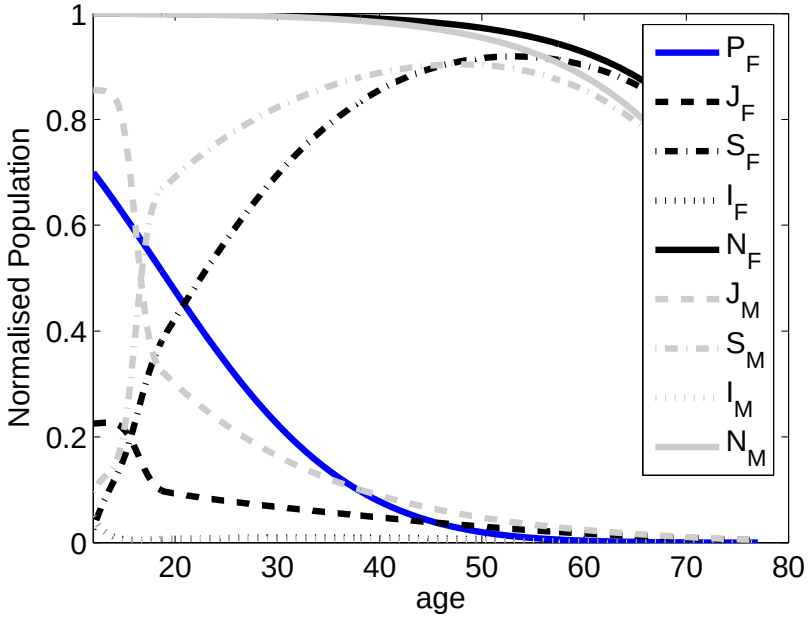
6.4.4 Model with Age-dependent Parameters, λ_i^h

We next move to the case of age-dependent parameters and λ_i^h, given in (6.3). The class profiles are shown in Figure 6-5 for the cases with and without protection. We see that the introduction of vaccination has a dramatic impact in this case, as it virtually eradicates infection. In comparison to the previous cases, Figure 6-5 shows a clear peak in infection when no protection is present. The juvenile classes decrease more slowly than with constant parameters. We use a smaller value of γ_i in this scenario, $\gamma_i = 0.8$, as the combination of age-dependent parameters and λ_i^h reduces the infected classes to an extremely low proportion even without infection.

A consideration of the proportion of infected individuals present in the model when there is a non-zero P_F class and when $P_F(a) = 0$ is shown in Figure 6-6. This shows that without protection, there is a peak in the proportion infected between the ages of 20 and 30, but the introduction of vaccination pushes the proportion of infected individuals (both male and female) to very low levels.

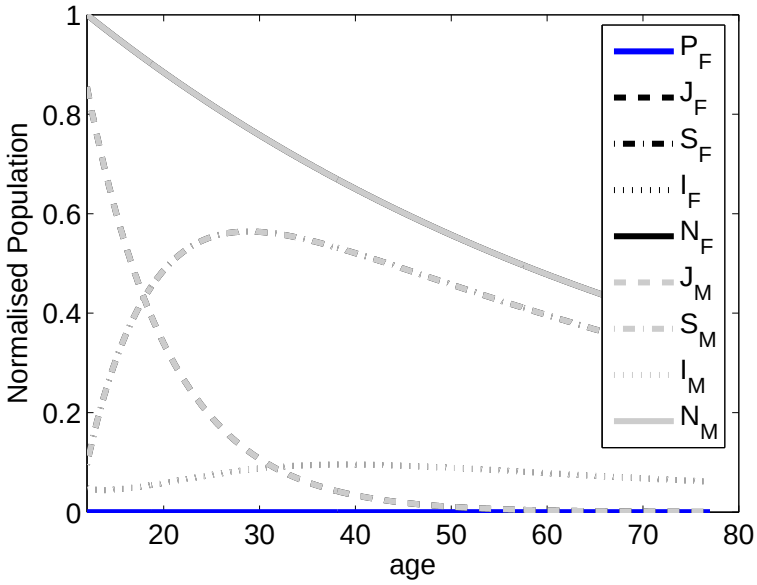


(a)

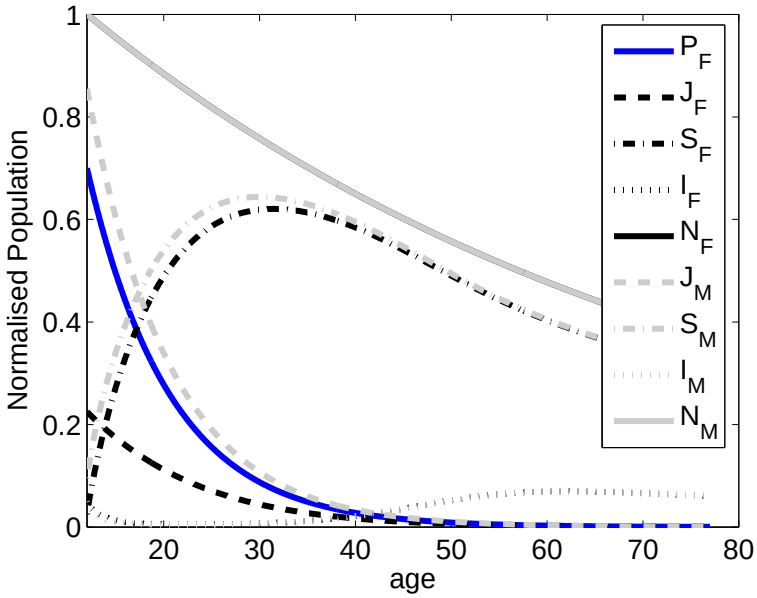


(b)

Figure 6-3: A graph showing all classes of the model with age-dependent parameter values and λ_i^l. The parameter values and initial conditions are as described in Table 3.2 and in this Chapter, with $\gamma_i = 0.8$. Figure 6-3a shows the system when there is no protected class and Figure 6-3b shows the system with a protected class and an average duration of immunity from vaccination of 10 years.

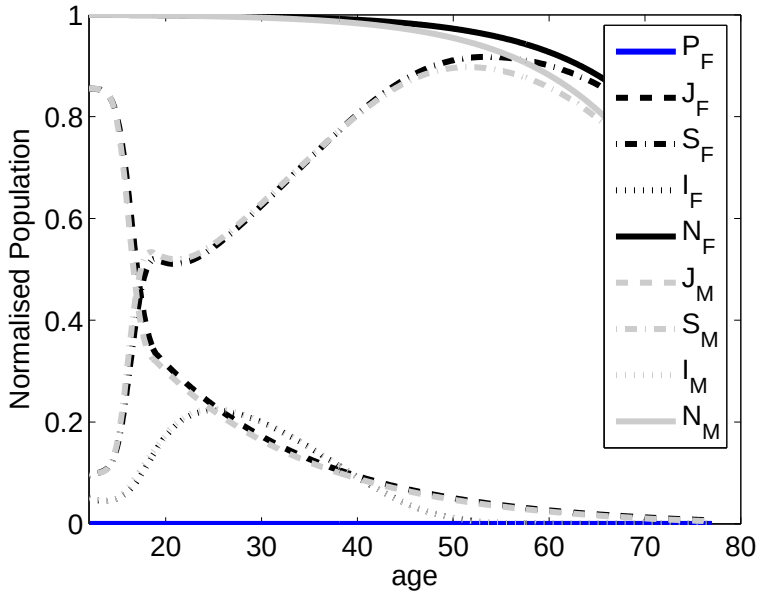


(a)

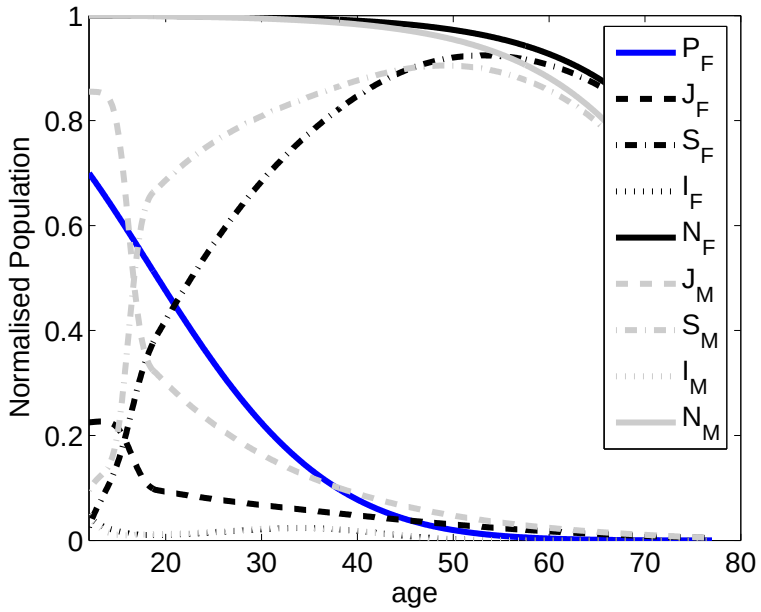


(b)

Figure 6-4: A graph showing all classes of the model with constant parameter values and λ_i^h. The parameter values and initial conditions are as described in Table 3.2 and in this Chapter, with $\gamma_i = 1$. Figure 6-4a shows the system when there is no protected class (here the female classes lie underneath the male classes) and Figure 6-4b shows the system with a protected class and an average duration of immunity from vaccination of 10 years.



(a)



(b)

Figure 6-5: A graph showing all classes of the model with age-dependent parameter values and λ_i^h. The parameter values and initial conditions are as described in Table 3.2 and in this Chapter, with $\gamma_i = 0.8$. Figure 6-5a shows the system when there is no protected class and Figure 6-5b shows the system with a protected class and an average duration of immunity from vaccination of 10 years.

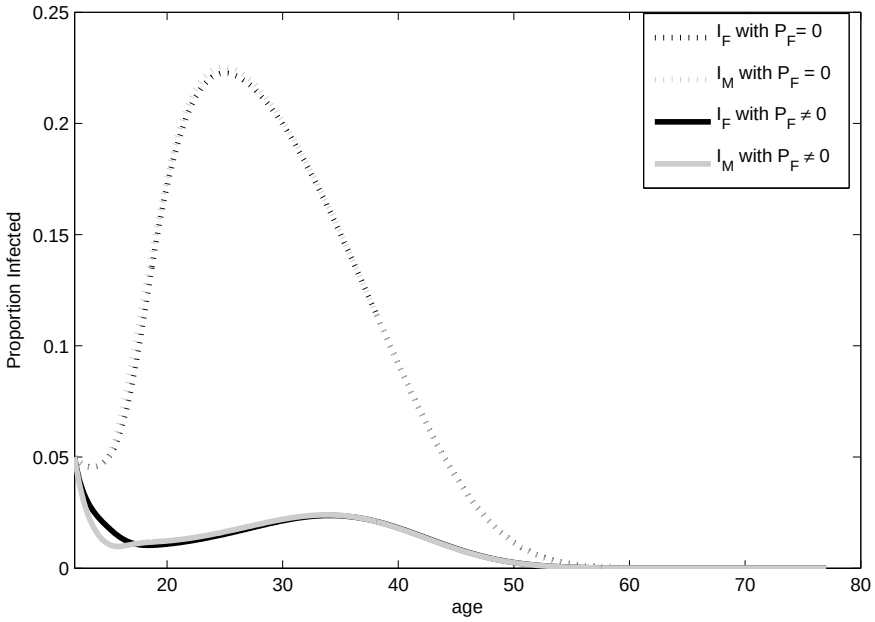


Figure 6-6: A graph showing the infected classes of the model with age-dependent parameter values and λ_i^h, both when a protected class exists and when there is no protected class. The parameter values and initial conditions are as described in Table 3.2 and in this chapter with $\gamma_i = 0.8$.

6.5 The PDE Model

We present a system incorporating age-dependence. This model takes age a_0 as its initial age, and divides the population into three or four classes, depending on whether they are male or female (M or F). In the male population, every individual is either classified as susceptible, 'juvenile' (i.e. non-sexually active) or infected at age a. In the female population a fourth class is added; that of protected individuals, who have been vaccinated. A schematic of this can be seen in Fig. 6-1.

6.5.1 The Model

Using the age-dependent parameter functions as outlined in Chapter 3, the model becomes

$$\frac{\partial P_F}{\partial t} + \frac{\partial P_F}{\partial a} = -(\alpha(a) + \mu_F(a))P_F(a,t), \tag{6.8a}$$

$$\frac{\partial J_F}{\partial t} + \frac{\partial J_F}{\partial a} = q(\alpha)\alpha(a)P_F(a,t) - (\eta_F(a) + \mu_F(a))J_F(a,t), \tag{6.8b}$$

$$\frac{\partial S_F}{\partial t} + \frac{\partial S_F}{\partial a} = (1-q(\alpha))\alpha(a)P_F(a,t) + \eta_F(a)J_F(a,t) + \gamma_F I_F(a,t) - (\lambda_F(a,t) + \mu_F(a))S_F(a,t), \tag{6.8c}$$

$$\frac{\partial I_F}{\partial t} + \frac{\partial I_F}{\partial a} = \lambda_F(a,t)S_F(a,t) - (\gamma_F + \mu_F(a))I_F(a,t), \tag{6.8d}$$

$$\frac{\partial J_M}{\partial t} + \frac{\partial J_M}{\partial a} = -(\eta_M(a) + \mu_M(a))J_M(a,t), \tag{6.8e}$$

$$\frac{\partial S_M}{\partial t} + \frac{\partial S_M}{\partial a} = \eta_M(a)J_M(a,t) + \gamma_M I_M(a,t) - (\lambda_M(a,t) - \mu_M(a))S_M(a,t), \tag{6.8f}$$

$$\frac{\partial I_M}{\partial t} + \frac{\partial I_M}{\partial a} = \lambda_M(a,t)S_M(a,t) - (\gamma_M + \mu_M(a))I_M(a,t), \tag{6.8g}$$

$$\frac{\partial N_F}{\partial t} + \frac{\partial N_F}{\partial a} = -\mu_F(a)N_F, \tag{6.8h}$$

$$\frac{\partial N_M}{\partial t} + \frac{\partial N_M}{\partial a} = -\mu_M(a)N_M. \tag{6.8i}$$

As our model is age- as well as time-dependent, we cannot define a single R_0 value; rather we can define a series of R_0 values based on the age of the initial infected individual in an otherwise susceptible population [31]. Assuming the age of the initial infected individual is $a^{'}$, R_0 for our model is,

$$R_{0,a'} = \frac{z(a^{'})^2}{(\gamma_F + 1/\phi)(\gamma_M + 1/\phi)} \left[\int_{a_0}^{a_{max}} \beta(a^{'}, a)\mathrm{d}a\right]^2. \tag{6.9}$$

All classes are as defined in previous Chapters and we set

$$\lambda_i(a,t) = z_i(a) \int_{a_0}^{a_{max}} \frac{\beta(a,a')I_k(a',t)}{N_k(a',t) - J_k(a',t)} \ \mathrm{d}a'. \tag{6.10}$$

Note that $i, k = M, F$ and $i \neq k$. As for the ODE model above, $\beta(a,a') = \beta A$ with β and A given in Chapter 3.

6.5.2 PDE Boundary Conditions

We assume here that $a_0 \leq a \leq a_{max}$, where $a_{max} \approx 77$ and $a_0 \approx 12$. The boundary conditions are the values for each of the classes at $a = a_0$ and are as follows (p, j_i as defined in Chapter 3):

- $P_F(a_0,t) = pN_F(a_0,t)$,
- $J_F(a_0,t) = (1-p)j_F N_F(a_0,t)$,
- $S_F(a_0,t) = (1-p)(1-j_F)N_F(a_0,t)$,
- $I_F(a_0,t) = 0$,
- $J_M(a_0,t) = j_M N_M(a_0,t)$,
- $S_M(a_0,t) = (1-j_M)N_M(a_0,t)$,
- $I_M(a_0,t) = 0$,
- $N_i(a_0,t) = N_i a_0$.

Here, p is the proportion of girls that have been vaccinated by age a_0, and $(1-p)j_F$ and j_M represent the proportion of the population that are in the non-sexually active female or male class at age a_0 respectively.

6.5.3 Initial Conditions

We assume, at $t = 0$, that vaccination only takes place at $a = a_0$. To calculate the initial conditions for the J_i ($i = F, M$) classes we neglect death rate and (since $P_F(a,0) = 0$, $a \neq a_0$) any connection to the protected class. We leave $J_i(a,0)$ as differential equations with respect to age, giving us $\frac{\mathrm{d}J_i}{\mathrm{d}a} = -\eta_i(a)J_i$. As we also assume no transfer of infection at the instant $t = 0$, we take $\frac{\mathrm{d}S_i}{\mathrm{d}a} = \eta_i(a)J_i$. We define $I_i(a,0)$ as $I_i^0(a)$ - we not do not define it further at present, but will estimate it from the data when calculating numerical solutions. The initial conditions for the N_i classes are

estimated to be Gompertz functions in [31]; the exact values as given below are from [61]. The initial conditions are listed below.

- $P_F(a,0) = 0, a \neq a_0$,
- $\frac{\mathrm{d}J_F}{\mathrm{d}a} = -\eta_F(a)J_F$,
- $\frac{\mathrm{d}S_F}{\mathrm{d}a} = \eta_F(a)J_F$,
- $I_F(a,0) = I_F^0(a)$,
- $\frac{\mathrm{d}J_M}{\mathrm{d}a} = -\eta_M(a)J_M$,
- $\frac{\mathrm{d}S_M}{\mathrm{d}a} = \eta_M(a)J_M$,
- $I_M(a,0) = I_M^0(a)$,
- $N_F(a,0) = e^{-(0.000189e^{0.1a})}$,
- $N_M(a,0) = e^{-(0.000354e^{0.098a})}$.

It is also important that the boundary conditions for $t = 0$ are equal to the initial conditions at $a = a_0$.

6.6 Analysis

6.6.1 Characteristic Equations

Using the Method of Characteristics as shown in [69] and parametrising about a variable s we can calculate the characteristics. We first arrange (6.8) into the form

$$\frac{\partial H_i}{\partial t} + \frac{\partial H_i}{\partial a} + \mu_i H_i = G_k(H_i), \tag{6.11}$$

where $i = F, M$ and $k = 1, ..., 7$, in order to calculate the characteristics and H_i represents the different classes (the G_k are functions).

We set

$$\frac{\mathrm{d}H_i(s+a-t,s)}{\mathrm{d}s} = \frac{\partial H_i(s+a-t,s)}{\partial t} + \frac{\partial H_i(s+a-t,s)}{\partial a}, \tag{6.12}$$

giving

$$\frac{\mathrm{d}H_i(s+a-t,s)}{\mathrm{d}s} + \mu_i(s+a-t)H_i(s+a-t,s) = G_k(H_i). \tag{6.13}$$

Using an integrating factor, we can then solve the equations for $a < t$ and $a \geq t$. On doing this, and setting $H_i(a,0) = H_i^0$, the characteristics are

$$P_F = \begin{cases} e^{-\int_0^t \mu_F(\tau+a-t)\mathrm{d}\tau} P_F^0(a-t) & \\ + \int_0^t e^{-\int_s^t \mu_F(\tau+a-t)\mathrm{d}\tau}(-\alpha(s+a-t)P_F(s+a-t,s)) \quad \mathrm{d}s & a \geq t \\ P_F(a_0,(a_0-a)+t)e^{-\int_{a_0}^a \mu_F(\tau)\mathrm{d}\tau} & \\ + \int_{a_0}^a e^{-\int_s^a \mu_F(\tau)\mathrm{d}\tau}(-\alpha(s)P_F(s,s+t-a)) \quad \mathrm{d}s & a < t \end{cases} \tag{6.14}$$

$$J_F = \begin{cases} e^{-\int_0^t \mu_F(\tau+a-t)\mathrm{d}\tau} J_F^0(a-t) & \\ + \int_0^t e^{-\int_s^t \mu_F(\tau+a-t)\mathrm{d}\tau}(q(\alpha)\alpha(s+a-t)P_F(s+a-t,s)) \quad \mathrm{d}s & \\ - \int_0^t e^{-\int_s^t \mu_F(\tau+a-t)\mathrm{d}\tau}\eta_F(s+a-t)J_F(s+a-t,s) \quad \mathrm{d}s & a \geq t \\ J_F(a_0,(a_0-a)+t)e^{-\int_{a_0}^a \mu_F(\tau)\mathrm{d}\tau} & \\ + \int_{a_0}^a e^{-\int_s^a \mu_F(\tau)\mathrm{d}\tau}(q(\alpha)\alpha(s)P_F(s,s+t-a)) \quad \mathrm{d}s & \\ - \int_{a_0}^a e^{-\int_s^a \mu_F(\tau)\mathrm{d}\tau}\eta_F(s)J_F(s,s+t-a) \quad \mathrm{d}s & a < t \end{cases} \tag{6.15}$$

$$S_F = \begin{cases} e^{-\int_0^t \mu_F(\tau+a-t)\mathrm{d}\tau} S_F^0(a-t) & \\ + \int_0^t e^{-\int_s^t \mu_F(\tau+a-t)\mathrm{d}\tau}((1-q(\alpha))\alpha(s+a-t)P_F(s+a-t,s)) \quad \mathrm{d}s & \\ + \int_0^t e^{-\int_s^t \mu_F(\tau+a-t)\mathrm{d}\tau}(\eta_F(s+a-t)J_F(s+a-t,s)) \quad \mathrm{d}s & \\ + \int_0^t e^{-\int_s^t \mu_F(\tau+a-t)\mathrm{d}\tau}\gamma_F I_F(s+a-t,s) \quad \mathrm{d}s & \\ - \int_0^t e^{-\int_s^t \mu_F(\tau+a-t)\mathrm{d}\tau}(\lambda_F(s+a-t,s)S_F(s+a-t,s)) \quad \mathrm{d}s & a \geq t \\ S_F(a_0,(a_0-a)+t)e^{-\int_{a_0}^a \mu_F(\tau)\mathrm{d}\tau} & \\ + \int_{a_0}^a e^{-\int_s^a \mu_F(\tau)\mathrm{d}\tau}((1-q(\alpha))\alpha(s)P_F(s,s+t-a)) \quad \mathrm{d}s & \\ + \int_{a_0}^a e^{-\int_s^a \mu_F(\tau)\mathrm{d}\tau}\eta_F(s)J_F(s,s+t-a)) \quad \mathrm{d}s & \\ + \int_{a_0}^a e^{-\int_s^a \mu_F(\tau)\mathrm{d}\tau}\gamma_F I_F(s,s+t-a) \quad \mathrm{d}s & \\ - \int_{a_0}^a e^{-\int_s^a \mu_F(\tau)\mathrm{d}\tau}(\lambda_F(s,s+t-a)S_F(s,s+t-a)) \quad \mathrm{d}s & a < t \end{cases} \tag{6.16}$$

$$I_F = \begin{cases} e^{-\int_0^t \mu_F(\tau+a-t)\mathrm{d}\tau} I_F^0(a-t) & \\ + \int_0^t e^{-\int_s^t \mu_F(\tau+a-t)\mathrm{d}\tau}(\lambda_F(s+a-t,s)S_F(s+a-t,s)) \quad \mathrm{d}s & \\ - \int_0^t e^{-\int_s^t \mu_F(\tau+a-t)\mathrm{d}\tau}(\gamma_F I_F(s+a-t,s)) \quad \mathrm{d}s & a \geq t \\ I_F(a_0,(a_0-a)+t)e^{-\int_{a_0}^a \mu_F(\tau)\mathrm{d}\tau} & \\ + \int_{a_0}^a e^{-\int_s^a \mu_F(\tau)\mathrm{d}\tau}(\lambda_F(s,s+t-a)S_F(s,s+t-a)) \quad \mathrm{d}s & \\ - \int_{a_0}^a e^{-\int_s^a \mu_F(\tau)\mathrm{d}\tau}(\gamma_F I_F(s,s+t-a)) \quad \mathrm{d}s & a < t \end{cases} \tag{6.17}$$

$$J_M = \begin{cases} e^{-\int_0^t \mu_F(\tau+a-t)\mathrm{d}\tau} J_M^0(a-t) \\ + \int_0^t e^{-\int_s^t \mu_F(\tau+a-t)\mathrm{d}\tau}(-\eta_M(s+a-t)J_M(s+a-t,s)) \quad \mathrm{d}s & a \geq t \\ J_M(a_0,(a_0-a)+t)e^{-\int_{a_0}^a \mu_F(\tau)\mathrm{d}\tau} \\ + \int_{a_0}^a e^{-\int_s^a \mu_F(\tau)\mathrm{d}\tau}(-\eta_M(s)J_M(s,s+t-a)) \quad \mathrm{d}s & a < t \end{cases} \tag{6.18}$$

$$S_M = \begin{cases} e^{-\int_0^t \mu_F(\tau+a-t)\mathrm{d}\tau} S_M^0(a-t) \\ + \int_0^t e^{-\int_s^t \mu_F(\tau+a-t)\mathrm{d}\tau}(\eta_M(s+a-t)J_M(s+a-t,s)) \quad \mathrm{d}s \\ + \int_0^t e^{-\int_s^t \mu_F(\tau+a-t)\mathrm{d}\tau}(\gamma_M I_M(s+a-t,s)) \quad \mathrm{d}s \\ - \int_0^t e^{-\int_s^t \mu_F(\tau+a-t)\mathrm{d}\tau}(\lambda_M(s+a-t,s)S_M(s+a-t,s)) \quad \mathrm{d}s & a \geq t \\ S_M(a_0,(a_0-a)+t)e^{-\int_{a_0}^a \mu_F(\tau)\mathrm{d}\tau} \\ + \int_{a_0}^a e^{-\int_s^a \mu_F(\tau)\mathrm{d}\tau}(\eta_M(s)J_M(s+t-a,s)) \quad \mathrm{d}s \\ + \int_{a_0}^a e^{-\int_s^a \mu_F(\tau)\mathrm{d}\tau}(\gamma_M I_M(s+t-a,s)) \quad \mathrm{d}s \\ - \int_{a_0}^a e^{-\int_s^a \mu_F(\tau)\mathrm{d}\tau}\lambda_M(s+t-a,s)S_M(s+t-a,s)) \quad \mathrm{d}s & a < t \end{cases} \tag{6.19}$$

$$I_M = \begin{cases} e^{-\int_0^t \mu_F(\tau+a-t)\mathrm{d}\tau} I_M^0(a-t) \\ + \int_0^t e^{-\int_s^t \mu_F(\tau+a-t)\mathrm{d}\tau}(\lambda_M(s+a-t,s)S_M(s+a-t,s)) \quad \mathrm{d}s \\ - \int_0^t e^{-\int_s^t \mu_F(\tau+a-t)\mathrm{d}\tau}(\gamma_M I_M(s+a-t,s)) \quad \mathrm{d}s & a \geq t \\ I_M(a_0,(a_0-a)+t)e^{-\int_{a_0}^a \mu_F(\tau)\mathrm{d}\tau} \\ + \int_{a_0}^a e^{-\int_s^a \mu_F(\tau)\mathrm{d}\tau}(\lambda_M(s,s+t-a)S_M(s,s+t-a)) \quad \mathrm{d}s \\ - \int_{a_0}^a e^{-\int_s^a \mu_F(\tau)\mathrm{d}\tau}(\gamma_M I_M(s,s+t-a)) \quad \mathrm{d}s & a < t \end{cases} \tag{6.20}$$

6.6.2 Numerical Solutions

In order to retrieve numerical solutions, we estimate the initial and boundary conditions from available data. $P_F(a,0)$ is a smoothed approximation for current government policy [2]; $S_i(a,0)$ and $J_i(a,0)$ are estimated using [3], $I_i(a,0)$ is estimated using data given in [63], and $N_i(a,0)$ are estimated in [61]. The initial conditions are therefore estimated to be

- $N_F(a,0) = e^{-(0.0000189e^{0.1(a)})}$,
- $N_M(a,0) = e^{-(0.0000354e^{0.098(a)})}$,
- $P_F(a,0) = \begin{cases} pN_F(a,0)(1 - \frac{0.9}{(1+exp(16.3-a))})cos(\pi l)^3 & a < 21 \\ 0 & a \geq 21. \end{cases}$
  where $l = \frac{4736(a-12)}{76657}$,

- $J_F(a,0) = ((1 - \frac{0.9}{(1+exp(16.3-a))})N_F(a,0) - P_F(a,0))$,
- $I_F(a,0) = (0.23e^{-(\frac{(a-21.8)}{12.5})^2})(\frac{0.9}{(1+exp(16.3-a))})N_F(a,0)$,
- $S_F(a,0) = (1 - 0.23e^{-(\frac{(a-21.8)}{12.5})^2})(\frac{0.9}{(1+exp(16.3-a))})N_F(a,0)$,
- $S_M(a,0) = (1 - 0.23e^{-(\frac{(a-21.8)}{12.5})^2})(\frac{0.9}{(1+exp(13.3-0.8a))})N_M(a,0)$,
- $J_M(a,0) = (1 - \frac{0.9}{(1+exp(13.3-0.8a))})N_M(a,0)$,
- $I_M(a,0) = (0.23e^{-(\frac{(a-21.8)}{12.5})^2})(\frac{0.9}{(1+exp(13.3-0.8a))})N_M(a,0)$.

Analysis of the PDE is difficult, as we see in the previous subsection, but it is possible to generate numerical solutions for the PDE. We numerically solve (6.8) using a finite difference scheme given in Appendix B (using [70]) to predict the distribution of each class. Figure 6-7 shows three graphs, the first (6-7a) showing the initial class distributions, 6-7b showing the distributions after 25 years and 6-7c showing the distributions after 40 years. They show that vaccination at 70% for the initial age class can virtually eradicate the disease in both males and females over a 40 year period.

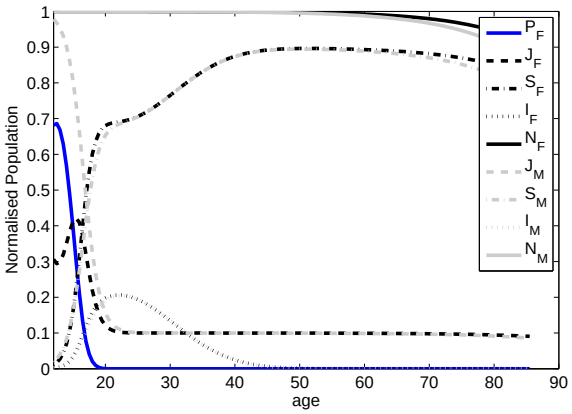
Figure 6-8 shows the female infection class profile after 25 and 50 years for varying values of $\alpha(a)$. After 25 years the greatest difference is between the profile when there is an average of 5 years protection and the other profiles. After 50 years, that difference is much more pronounced and we also see a larger difference between the infection profile with a 10 year vaccine and the infection profiles with 20 and 40 year vaccines. With the latter two, female infection is almost eradicated after 50 years.

Figure 6-9 shows the varying female infection profiles after 25 years when we vary the value of p. This figure shows that the value of p has a large impact on the infection profile, with the higher values of p leading to much lower peaks in the infection profile after 25 years.

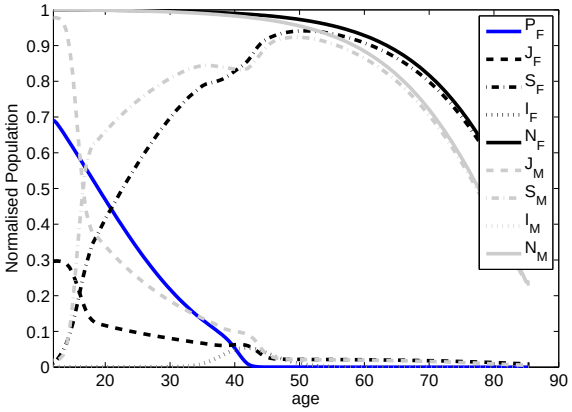
6.7 Conclusions

In this Chapter we have introduced age-dependence to our system. We initially studied an age-dependent ODE model, in a variety of situations. We were able to partially analyse this model and found expressions for the $P_F(a)$, $J_i(a)$ and $N_i(a)$ classes.

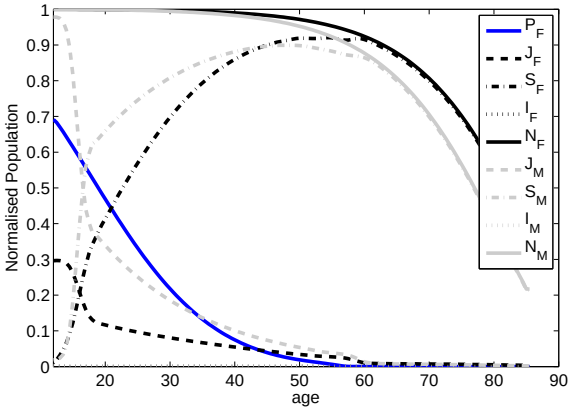
Figures 6-2 - 6-5 show the age-dependent ODE in a number of ways, varying both the choice of λ_i and the functions used for the parameters. In all cases, infection was shown to persist (albeit potentially at very low levels) despite the introduction of vaccination, although the infected class profiles are particular to each situation. From



(a)

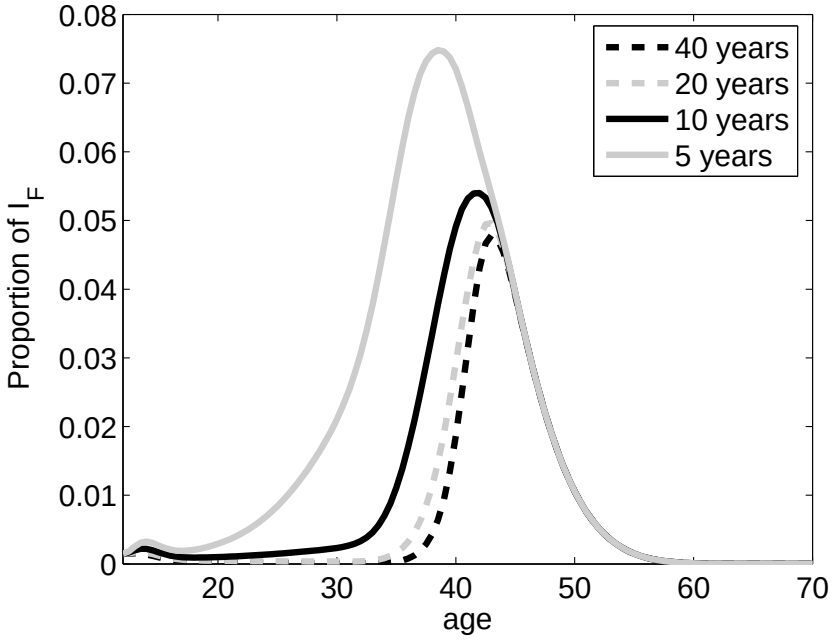


(b)

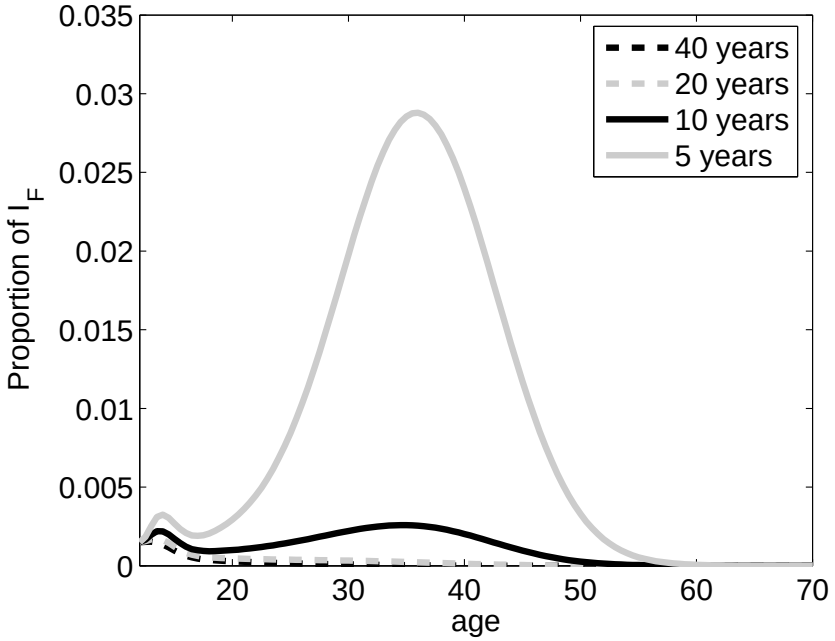


(c)

Figure 6-7: Numerical solutions of the PDE model initially (Figure 6-7a), after 25 years (Figure 6-7b) and after 40 years (Figure 6-7c). The initial conditions and parameter values are described in Chapter 3, with $\gamma_i = 0.8$.



(a)



(b)

Figure 6-8: Graphs of I_F as α varies after 25 (Figure 6-8a) and 50 (Figure 6-8b) years. All other parameters and initial and boundary conditions are as described in this Chapter and Chapter 3, with $\gamma_i = 0.8$.

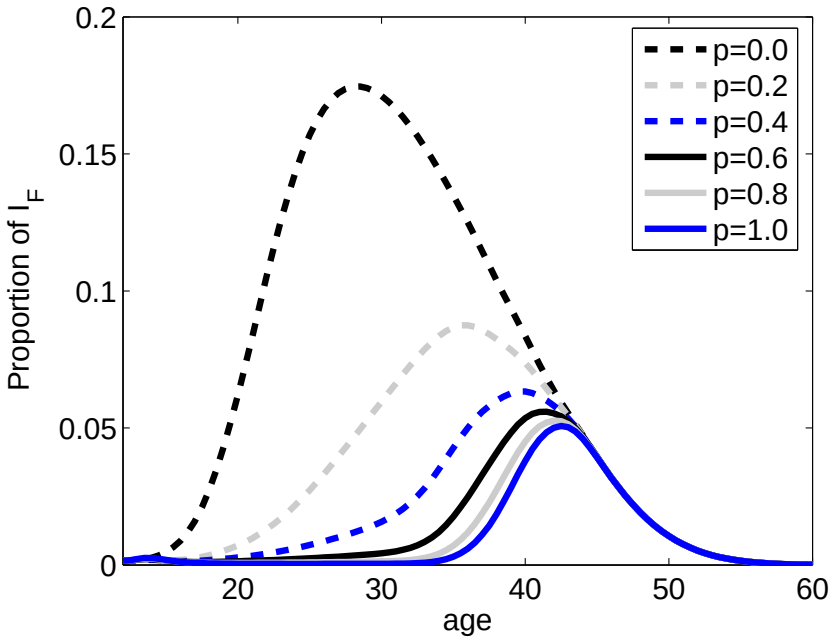


Figure 6-9: A graph of I_F as p varies after 25 years. All other parameters and initial and boundary conditions are as described in this chapter and Chapter 3.

a modelling perspective, these results show that it is possible to generate very different outcomes from the same model, dependent on the form of the parameters and force of infection. The case illustrated by Fig 6-5 is the most accurate of the four ODE cases studied, and the results found most closely emulate those shown when the PDE is solved numerically. In drawing a conclusion, these results show the choice of model and model parameters can influence any predictions. Our conclusions from Figure 6-5 suggest that the introduction of vaccination means that it is possible to virtually eradicate the disease.

We were able to find the characteristics for the PDE using the Method of Characteristics. We were able to describe the forms of the characteristics, using the method presented in [69]; defining the characteristics in this way means that further analytical work may be more straightforward.

The numerical solutions in Figure 6-7 for the PDE show that, over time, the introduction of a protected class has the ability to eradicate the infection from the population. The initial conditions for this system can be seen in Figure 6-7a and show the profile for the infected classes as vaccination is introduced. Figure 6-7c suggests that, 40 years after the introduction of the vaccine, the disease has almost been eradicated. This result is supported by the results from the age-dependent ODE with age-dependent

parameters and λ_i^h, and can also be matched to the time-dependent ODE presented in Chapter 5 for a non-standard parameter set (i.e. when $z = 1.7$). These results suggest that current vaccination policy may be sufficient to virtually eradicate HPV from the population in 40 years. Figures 6-8 and 6-9 show the influence α and p have on the female infection profile over time. We see that, contrary to the time-dependent ODE case, over 25 years p has a larger impact than α. Over a 50 year time span, we see that α has a large effect, with the smaller values of α able to drive female infection almost to eradication. We probably only see this difference after 50 years as the true impact of the longer-lasting vaccines will only become apparent over a longer time period. The following Chapters will now assess the cost-effectiveness of that vaccination strategy, and whether there is a more cost-effective way to deliver the vaccine.

Chapter 7

Optimal Control applied to an ODE Model

7.1 Introduction

The introduction of the HPV vaccine generated much debate about its value for money, and the most cost-effective way to deliver it. This is discussed in some detail in Chapter 1. Several analyses of the cost-effectiveness of the HPV vaccine have been carried out; the models all produce slightly different results dependent upon the assumptions made in each model, but almost all agree that female-only vaccination is more cost-effective than vaccinating both males and females [12, 22, 37]. Here we take a different approach to previous models - we explore the solution of an optimal control problem in which we minimise the costs associated with both treatment of infecteds and the vaccination programme, subject to the underlying infection dynamics.

We present a detailed description of previous optimal control work in Chapter 1. Optimal control has been applied to infectious disease problems in the past, and is a good method for determining how best to control a disease. Sethi and Staats [47] and [46] both provide an overview of optimal control as applied to some deterministic models, including a situation with vaccination. Ögren and Martin [49] apply optimal control to structured *SIR* models to determine the optimal vaccination policy for populations that are very mobile, making their minimisation problem one that considers both the proportion who fall ill and the cost of the vaccine. Lenhart and Workman [44] introduce many examples of optimal control applied to different problems, including an infectious disease problem.

The notation we use to develop an optimal control model follows that given in [44],

in that we define the differential equation (state equation) to be

$$x^{'}(t) = g(t, x(t), u(t)), \tag{7.1}$$

with control $u(t)$ acting on it ($x(t)$ and $u(t)$ can either be single variables or vectors of variables $[y_1, ..., y_n]$). The objective functional is defined to be

$$J(u) := \int_{t_0}^{t_1} f(t, x(t), u(t))dt. \tag{7.2}$$

We are interested in either minimising or maximising (depending on the exact problem being considered) the objective functional subject to (7.1) - i.e. in finding the optimal functions $u^*(t)$ and $x^*(t)$ such that (7.2) is either maximised or minimised. We can do this by using Pontryagin's Maximum Principle. As stated in [44], this is

Theorem 1 *If $u^*(t)$ and $x^*(t)$ are optimal for*

$$\max_{\mathrm{u}} \quad \int_{t_0}^{t_1} f(t, x(t), u(t)) \quad \mathrm{d}t$$

subject to

$$\begin{aligned} x^{'}(t) &= g(t, x(t), u(t)) \\ x(t_0) &= x_0 \quad and \quad x(t_1) \quad free. \end{aligned}$$

then there exists a piecewise differentiable adjoint variable $\lambda(t)$ such that

$$H(t, x^*(t), u(t), \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t))$$

for all controls u at each time t, where the Hamiltonian H is

$$H = f(t, x(t), u(t)) + \lambda(t)g(t, x(t), u(t)),$$

and

$$\begin{aligned} \lambda^{'}(t) &= -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x} \\ \lambda(t_1) &= 0. \end{aligned}$$

By defining the Hamiltonian as in the Theorem above, we can find $u^*(t)$ through differentiation; $\frac{\partial H}{\partial u} = 0$ at $u^*(t)$. This will generally depend on the adjoint equation, which we can find as described in the Theorem. Once we have found $u^*(t)$, we can

substitute it into the state equation (7.1) to find $x^*(t)$.

Returning to the problem described above in (7.1) and (7.2) and following Pontryagin's Maximum Principle as stated above, we find the Hamiltonian to be

$$H(t, x, u, \lambda) := f(t, x, u) + \lambda g(t, x, u).$$

From here we can deduce the optimality condition, the adjoint equation and the transversality condition, all of which will be used in determining the optimal control, $u^*(t)$. The optimality condition is

$$\frac{\partial H}{\partial u} \mid_{u^*} = 0 \quad \Rightarrow \quad f_u + \lambda g_u \mid_{u^*} = 0,$$

(note that the problem is a minimisation problem if H is convex, i.e. if $\frac{\partial^2 H}{\partial u^2} > 0$ and a maximisation problem if H is concave, i.e. if $\frac{\partial^2 H}{\partial u^2} < 0$ [44]), with adjoint equation

$$\lambda^{'} = -\frac{\partial H}{\partial x} \qquad \Rightarrow \qquad \lambda^{'} = -(f_x + \lambda g_x),$$

and transversality condition

$$\lambda(t_1) = 0.$$

Finally, the state equation can also be described as

$$x^{'}(t) = g(t, x, u) = \frac{\partial H}{\partial \lambda}, \quad x(t_0) = x_0.$$

From the optimality equation we can find u^*, thus giving us the form of the optimal control function.

We present a model which allows for vaccination of both an adolescent female population and a catch-up programme for vaccination of females in their late teens. Parameters linked to costs and underlying infection dynamics are estimated from a range of published sources. We compare our results to a system with constant control, and one allowing for male vaccination, to show how these alternative scenarios impact on the optimal control solution.

7.2 Model

We construct an optimal control problem, for which the objective functional which we wish to minimise is the total cost associated with HPV infection within a closed population and the related vaccination programme. This functional is constrained by the underlying infection dynamics within the population, which are represented by a

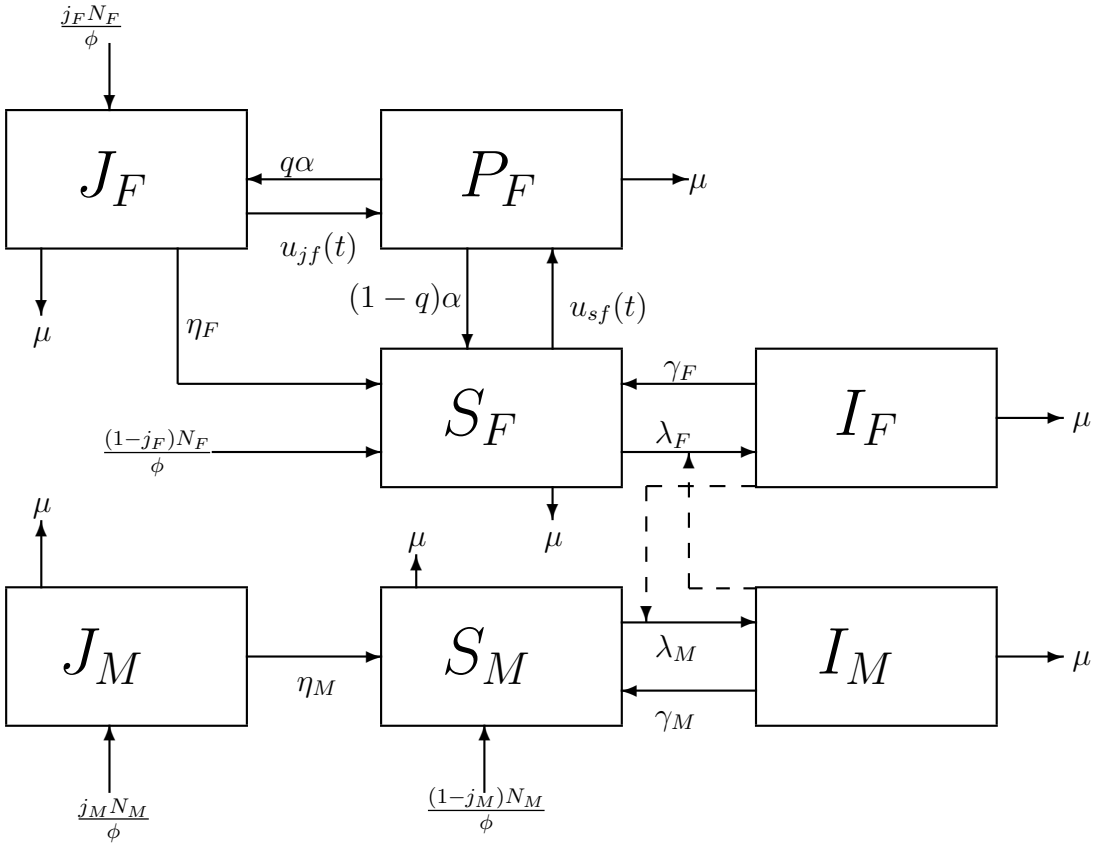


Figure 7-1: Schematic of the model system. It shows the basic dynamics of the model and the controls $u_{jf}(t)$ and $u_{sf}(t)$ which move individuals from the non-sexually active female class to the protected female class and from the sexually active female class to the protected female class respectively. The force of infection is $\lambda_i = z\beta I_k/(N_k - J_k)$ (z, β defined in Table 3.2, $i, k = F, M$, $i \neq k$).

compartmental model in which the individuals are classified according to gender and infection status, as for our model of infection dynamics in Chapter 5.

We present a slightly different model to previous Chapters, although we include the same classes as in Chapter 5. In this case, individuals enter the model either through the non-sexually active class or the susceptible class. Individuals then leave these classes and enter the protected class at a rate $u_{jf}(t)$ or $u_{sf}(t)$ - these are the controls acting on the non-sexually active and sexually active female classes respectively.

The model schematic is given in Figure 7-1. All parameters used in the model are defined, and their ranges given, in Table 3.2. The rates of vaccination of the non-sexually active and the sexually active classes are $u_{jf}(t)$ and $u_{sf}(t)$ respectively. Combining these assumptions produces the following model system for HPV infection:

$$\frac{\mathrm{d}J_F}{\mathrm{d}t} = \frac{j_F N_F}{\phi} + \alpha q(\alpha) P_F - (u_{jf}(t) + \eta_F + \frac{1}{\phi}) J_F, \tag{7.3a}$$

$$\frac{\mathrm{d}S_F}{\mathrm{d}t} = \frac{(1-j_F)N_F}{\phi} + \eta_F J_F - \lambda_F S_F + \gamma_F I_F - (u_{sf}(t) + \frac{1}{\phi}) S_F + (1-q(\alpha))\alpha P_F, \tag{7.3b}$$

$$\frac{\mathrm{d}P_F}{\mathrm{d}t} = u_{jf}(t) J_F + u_{sf}(t) S_F - (\alpha + \frac{1}{\phi}) P_F, \tag{7.3c}$$

$$\frac{\mathrm{d}I_F}{\mathrm{d}t} = \lambda_F S_F - (\gamma_F + \frac{1}{\phi}) I_F, \tag{7.3d}$$

$$\frac{\mathrm{d}J_M}{\mathrm{d}t} = \frac{j_m N_M}{\phi} - (\eta_M + \frac{1}{\phi}) J_M, \tag{7.3e}$$

$$\frac{\mathrm{d}S_M}{\mathrm{d}t} = \frac{(1-j_M)N_M}{\phi} + \eta_M J_M - \lambda_M S_M + \gamma_M I_M - \frac{1}{\phi} S_M, \tag{7.3f}$$

$$\frac{\mathrm{d}I_M}{\mathrm{d}t} = \lambda_M S_M - (\gamma_M + \frac{1}{\phi}) I_M. \tag{7.3g}$$

To completely specify the problem, we include initial conditions ($J_F(0) = 12500$, $S_F(0) = 103325$, $P_F(0) = 0$, $I_F(0) = 9175$, $J_M(0) = 12500$, $S_M(0) = 103325$, $I_M(0) = 9175$) which are based on data estimates of prevalence and sexual activity from a population prior to vaccination [3, 63].

In the absence of any control, R_0 is given as

$$R_0 = \frac{(z\beta)^2}{(\gamma_F + 1/\phi)(\gamma_M + 1/\phi)}. \tag{7.4}$$

7.2.1 Adding Optimal Control

We include optimal control in the model through the rates of vaccination, $u_{jf}(t)$ and $u_{sf}(t)$, which act on the non-sexually active ($J_F(t)$) and the sexually active ($S_F(t)$) female classes respectively. These controls ($u_{jf}(t)$ and $u_{sf}(t)$) represent the proportion of each class that is vaccinated per unit time (year). We set a maximum for both $u_{jf}(t)$ and $u_{sf}(t)$ that equates to 90% coverage, as this is a reasonable estimate for the maximum coverage that can be realistically achieved. The model parameters u_{jf} and u_{sf} are annual rates and hence 90% coverage corresponds to $max(u_n) = 2.3$, $n = jf, sf$. We calculate this by considering that the only way for individuals to leave (e.g.) the non-sexually active class is by vaccination, giving $J_F(t) = J_F(0)e^{-u_{jf}t}$. For a 90% annual vaccination rate, we therefore need to solve $0.1J_F(0) = J_F(0)e^{-u_{jf}}$, giving $u_{jf} = 2.3$.

The costs associated with vaccination appear as quadratic terms in the objective

functional. A quadratic term is chosen to describe the nonlinear behaviour of the cost of implementing a vaccination programme; per unit vaccinated it becomes more expensive to vaccinate once a higher proportion of the population is targeted [50]. The form of the objective functional follows previous applications of optimal control to the management of infectious diseases [44, 51, 52], as discussed in Chapter 1.

Combining the factors described above we obtain the optimal functional

$$\min_{\mathrm{u}} \quad J(u) = \int_0^T \left[AI_F(t) + cu_{jf}^2(t) + du_{sf}^2(t)\right] \ \mathrm{d}t, \tag{7.5}$$
$$u \in \{u_n : 0 \leq u_n \leq 2.3\}, n = jf, sf$$

subject to the underlying dynamics given in (7.3).

The weightings A, c and d relate to the costs of infection (A) and vaccination (c and d). The parameter A includes the cost of screening women and the cost of further tests and treatment in the case of a positive smear test. We include the probabilities of progression to pre-cancerous lesions, CIN and cancer with the cost of each stage to give an overall cost on infection, from [71]. To calculate c and d we use the cost of three doses of the vaccine plus the administration costs. To calculate these parameters we use data from [10] which suggests that the cost of vaccination is £60 per dose, with $\approx$ £3.56 pounds per dose administration costs when vaccination is administered through the school and $\approx$ £10 per dose administration costs when the vaccine is administered by a GP. We equate the cost of vaccination in schools to the cost of vaccinating non-sexually active individuals, and the cost of vaccination at GP surgeries to the cost of vaccinating sexually active individuals. On multiplying these costs by an estimated number of individuals in the appropriate class (non-sexually active and sexually active class respectively), we find the scaled estimates for these values are $A = 0.0002$, $c = 0.1$ and $d = 1$.

To understand the importance of using an optimal control approach, we compare results obtained with the system above to the output of a model which assumes a constant vaccination strategy. To do this, we replaced $u_{jf}(t)$ and $u_{sf}(t)$ with the constant p/ϕ, where ϕ is the average lifespan of individuals from the age of 12 and p is the proportion vaccinated in their lifetime (see Table 3.2 for parameter values).

To compare the current vaccination strategy with one which allows for vaccination of both sexes, we extend (7.3) to include two more controls $u_{jm}(t)$ and $u_{sm}(t)$ - vaccination of males in the non-sexually active and sexually active classes respectively. The revised model is given in Section 7.2.2. Since HPV-16 and -18 are rarely treated in males in the UK [8], we assume both that there is no cost to treating infected males (i.e. weighting

on $I_M(t)$ in the objective functional, B, is zero) and that there is a small cost associated to vaccinating males ($B = 0.0001$).

7.2.2 The Hamiltonian and Optimal Solution

Applying this theory specifically to the model presented in (7.3), we find that the Hamiltonian takes the form

$$\begin{aligned}
H = AI_F + cu_{jf}^2 + du_{sf}^2 + \lambda_1(\frac{j_F N_F}{\phi} - (\eta_F + u_{jf}(t) + \frac{1}{\phi})J_F + q(\alpha)\alpha P_F) \\
+ \lambda_2(\frac{(1-j_F)N_F}{\phi} + \eta_F J_F - \frac{z\beta S_F I_M}{N_M - J_M} + \gamma_F I_F - (u_{sf}(t) + \frac{1}{\phi})S_F + (1-q(\alpha))\alpha P_F) \\
+ \lambda_3(u_{jf}(t)J_F + u_{sf}(t)S_F - (\alpha + \frac{1}{\phi})P_F) + \lambda_4(\frac{z\beta S_F I_M}{N_M - J_M} - (\gamma_F + \frac{1}{\phi})I_F) \\
+ \lambda_5(\frac{j_M N_M}{\phi} - (\eta_M + \frac{1}{\phi})J_M) + \lambda_6(\frac{(1-j_M)N_M}{\phi} + \eta_M J_M - \frac{z\beta S_M I_F}{N_F - J_F} + \gamma_M I_M - \frac{1}{\phi}S_M) \\
+ \lambda_7(\frac{z\beta S_M I_F}{N_F - J_F} - (\gamma_M + \frac{1}{\phi})I_M).
\end{aligned}$$

The adjoint equations follow directly from this and are given as

$$\lambda_1' = (\eta_F + u_{jf}(t) + \frac{1}{\phi})\lambda_1 - \eta_F\lambda_2 - u_{jf}(t)\lambda_3 + \frac{z\beta S_M I_F}{(N_F - J_F)^2}\lambda_6 - \frac{z\beta S_M I_F}{(N_F - J_F)^2}\lambda_7, \tag{7.6a}$$

$$\lambda_2' = (\frac{z\beta I_M}{N_M - J_M} + u_{sf}(t) + \frac{1}{\phi})\lambda_2 - u_{sf}(t)\lambda_3 - \frac{z\beta I_M}{N_M - J_M}\lambda_4, \tag{7.6b}$$

$$\lambda_3' = -q(\alpha)\alpha\lambda_1 - (1-q(\alpha))\alpha\lambda_2 + (\alpha + \frac{1}{\phi})\lambda_3, \tag{7.6c}$$

$$\lambda_4' = -A - \gamma_F\lambda_2 + (\gamma_F + \frac{1}{\phi})\lambda_4 + \frac{z\beta S_M}{N_F - J_F}\lambda_6 - \frac{z\beta S_M}{N_F - J_F}\lambda_7, \tag{7.6d}$$

$$\lambda_5' = \frac{z\beta S_F I_M}{(N_M - J_M)^2}\lambda_2 - \frac{z\beta S_F I_M}{(N_M - J_M)^2}\lambda_4 + (\eta_M + \frac{1}{\phi})\lambda_5 - \eta_M\lambda_6, \tag{7.6e}$$

$$\lambda_6' = (\frac{z\beta I_F}{N_F - J_F} + \frac{1}{\phi})\lambda_6 - \frac{z\beta I_F}{N_F - J_F}\lambda_7, \tag{7.6f}$$

$$\lambda_7' = \frac{z\beta S_F}{N_M - J_M}\lambda_2 - \frac{z\beta S_F}{N_M - J_M}\lambda_4 - \gamma_M\lambda_6 + (\gamma_M + \frac{1}{\phi})\lambda_7, \tag{7.6g}$$

with transversality conditions $\lambda_w(T) = 0$ ($w = 1, ..., 7$, T is the end time). Using the Hamiltonian, we obtain the optimality conditions

$$u_{jf}^*(t) = \frac{(\lambda_1 - \lambda_3)J_F}{2c},$$

and

$$u^*_{sf}(t) = \frac{(\lambda_2 - \lambda_3)S_F}{2d}.$$

Including male vaccination

In order to judge whether it can be cost-effective to vaccinate males as well as females, we compare the model described above with one that includes male vaccination. This model includes another class, the protected male class $P_M(t)$, so the model is the same for both the male and female genders. This means the inclusion of another two controls on the male classes, $u_{jm}(t)$ and $u_{sm}(t)$, which mimic the controls described above in the female-only vaccination scenario. As mentioned above, the weighting on male infection is B, with $B = 0$ or $B = 0.0001$ in the numerical solutions. The problem with a male vaccinated class is as follows:

$$\min_{\mathrm{u}} \quad J(u) = \int_0^T [AI_F(t) + BI_M(t) + c(u^2_{jf}(t) + u^2_{jm}(t)) + d(u^2_{sf}(t) + u^2_{sm}(t))] \quad dt,$$
$$u \in \{u_b \colon 0 \leq u_b \leq 2.3\} \quad b = jf, sj, jm, sm,$$

subject to

$$\frac{\mathrm{d}J_F}{\mathrm{d}t} = \frac{j_F N_F}{\phi} + \alpha q(\alpha) P_F - (u_{jf}(t) + \eta_F + \frac{1}{\phi})J_F, \tag{7.7a}$$

$$\frac{\mathrm{d}S_F}{\mathrm{d}t} = \frac{(1 - j_F)N_F}{\phi} + \eta_F J_F - \lambda_F S_F + \gamma_F I_F - (u_{sf}(t) + \frac{1}{\phi})S_F + (1 - q(\alpha))\alpha P_F, \tag{7.7b}$$

$$\frac{\mathrm{d}P_F}{\mathrm{d}t} = u_{jf}(t)J_F + u_{sf}(t)S_F - (\alpha + \frac{1}{\phi})P_F, \tag{7.7c}$$

$$\frac{\mathrm{d}I_F}{\mathrm{d}t} = \lambda_F S_F - (\gamma_F + \frac{1}{\phi})I_F, \tag{7.7d}$$

$$\frac{\mathrm{d}J_M}{\mathrm{d}t} = \frac{j_M N_M}{\phi} + \alpha q(\alpha) P_M - (u_{jm}(t) + \eta_M + \frac{1}{\phi})J_M, \tag{7.7e}$$

$$\frac{\mathrm{d}S_M}{\mathrm{d}t} = \frac{(1 - j_M)N_M}{\phi} + \eta_M J_M - \lambda_M S_M + \gamma_M I_M - (u_{sm}(t) + \frac{1}{\phi})S_M + (1 - q(\alpha))\alpha P_M, \tag{7.7f}$$

$$\frac{\mathrm{d}P_M}{\mathrm{d}t} = u_{jm}(t)J_M + u_{sm}(t)S_M - (\alpha + \frac{1}{\phi})P_M, \tag{7.7g}$$

$$\frac{\mathrm{d}I_M}{\mathrm{d}t} = \lambda_M S_M - (\gamma_M + \frac{1}{\phi})I_M. \tag{7.7h}$$

We can generate the Hamiltonian, adjoint equations and characterise the optimal

control as before; the adjoint equations are

$$\lambda_1^{'} = (\eta_F + u_{jf}(t) + \frac{1}{\phi})\lambda_1 - \eta_F\lambda_2 - u_{jf}(t)\lambda_3 + \frac{z\beta S_M I_F}{(N_F - J_F)^2}\lambda_6 - \frac{z\beta S_M I_F}{(N_F - J_F)^2}\lambda_8, \tag{7.8a}$$

$$\lambda_2^{'} = (\frac{z\beta I_M}{N_M - J_M} + u_{sf}(t) + \frac{1}{\phi})\lambda_2 - u_{sf}(t)\lambda_3 - \frac{z\beta I_M}{N_M - J_M}\lambda_4, \tag{7.8b}$$

$$\lambda_3^{'} = -q(\alpha)\alpha\lambda_1 - (1 - q(\alpha))\alpha\lambda_2 + (\alpha + \frac{1}{\phi})\lambda_3, \tag{7.8c}$$

$$\lambda_4^{'} = -A - \gamma_F\lambda_2 + (\gamma_F + \frac{1}{\phi})\lambda_4 + \frac{z\beta S_M}{N_F - J_F}\lambda_6 - \frac{z\beta S_M}{N_F - J_F}\lambda_8, \tag{7.8d}$$

$$\lambda_5^{'} = (\eta_M + u_{jm}(t) + \frac{1}{\phi})\lambda_5 - \eta_M\lambda_6 - u_{jm}(t)\lambda_7 + \frac{z\beta S_F I_M}{(N_M - J_M)^2}\lambda_2 - \frac{z\beta S_F I_M}{(N_M - J_M)^2}\lambda_4, \tag{7.8e}$$

$$\lambda_6^{'} = (\frac{z\beta I_F}{N_F - J_F} + u_{sm}(t) + \frac{1}{\phi})\lambda_6 - u_{sm}(t)\lambda_7 - \frac{z\beta I_F}{N_F - J_F}\lambda_8, \tag{7.8f}$$

$$\lambda_7^{'} = -q(\alpha)\alpha\lambda_5 - (1 - q(\alpha))\alpha\lambda_6 + (\alpha + \frac{1}{\phi})\lambda_7, \tag{7.8g}$$

$$\lambda_8^{'} = -B - \gamma_M\lambda_6 + (\gamma_M + \frac{1}{\phi})\lambda_8 + \frac{z\beta S_F}{N_M - J_M}\lambda_2 - \frac{z\beta S_M}{N_M - J_M}\lambda_4, \tag{7.8h}$$

with transversality conditions $\lambda_q(T) = 0$ ($q = 1, ..., 8$, T is end time). The female optimal control functions are characterised as

$$u_{jf}^*(t) = \frac{(\lambda_1 - \lambda_3)J_F}{2c},$$

and

$$u_{sf}^*(t) = \frac{(\lambda_2 - \lambda_3)S_F}{2d}.$$

The male controls are

$$u_{jm}^*(t) = \frac{(\lambda_5 - \lambda_7)J_M}{2c},$$

and

$$u_{sm}^*(t) = \frac{(\lambda_6 - \lambda_7)S_M}{2d}.$$

7.3 Numerical Solutions

We solve the optimal control problems (both with and without male vaccination), comprising of the model equations, the adjoint equations and the optimal control functions using a numerical method as described in [44]. The Matlab code is given in Appendix B.

Figure 7-2 shows the solution profiles and control functions for $\alpha = 0.05$, $\alpha = 0.1$ and

$\alpha = 0.2$. As the duration of protection increases (α decreasing), both controls decrease, although $u_{jf}(t)$ is always less than $u_{sf}(t)$. For shorter durations of protection ($\alpha = 0.2$, $\alpha = 0.1$), over time the optimal solution is to vaccinate both the sexually active and non-sexually active classes, but to decrease the vaccination on the non-sexually active more rapidly (at first) than the vaccination on the sexually active (Figures 7-2b and 7-2d). For a 20 year vaccine ($\alpha = 0.05$), the decrease in vaccination for the non-sexually active females mirrors that for the sexually active class. This is because the vaccine will still be effective when these individuals become sexually active.

To understand more about the interplay between the two control approaches ($u_{jf}(t)$ and $u_{sf}(t)$), we solved the optimal control problem first by setting $u_{jf}(t) \equiv 0$ and looking at the resulting time profile for $u_{sf}(t)$ and then reversing the situation to consider $u_{jf}(t)$ with $u_{sf}(t) \equiv 0$. The numerical solution profiles which we obtained are shown in Figure 7-3. The two scenarios differ significantly. When $u_{jf}(t) \equiv 0$, $u_{sf}(t)$ deviates very little from the profile shown in Figure 7-2 for the corresponding α value. However, when $u_{sf}(t) \equiv 0$, $u_{jf}(t)$ begins at the maximum level of control, and is maintained at a higher value for longer (compared to Figure 7-2). With longer lasting protection, vaccine coverage for the non-sexually active class increases (compared to Figure 7-3d), which results in slightly lower infection levels (compared to Figure 7-3c), but these levels are still much higher than with the vaccination of sexually active individuals only (Figure 7-3a).

As the cost of catch-up vaccination for sexually active individuals increases, there is a response through the vaccination of non-sexually active individuals. As shown in Figure 7-4, the more costly the catch-up programme (d increasing), the higher the vaccination of non-sexually active individuals should be.

7.3.1 Constant Control

Figure 7-5 provides a comparison between the optimal control problem and a constant control problem for two values of the contact parameter z. In both cases infection is reduced to very low levels, although with low z (Figures 7-5a and 7-5b), the optimal control problem has a significantly lower protected class than the optimal control problem with a higher z value. For both values of z the constant control model has a much larger protected class than the optimal control problem.

7.3.2 Male Vaccination

The inclusion of male vaccination produces interesting results which we present in Figure 7-6. Despite little or no cost associated with male infection, the optimal control

solution maintains a vaccination programme for males which, in the case of the non-sexually active individuals, exceeds that for the females. For sexually active individuals, control on the males shadows that for the females. When we set $B = 0.0001 = A/2$, we see that the male and female controls are extremely similar in their behaviour. In all cases, the lowest rate of vaccination is that for the non-sexually active females and the highest rate is for sexually active females, with the male vaccination rates falling between these two extremes.

7.4 Adding Natural Immunity

As in Chapter 5, we now add natural immunity to the model to see if this impacts on our results. Gaff and Schaefer [50] found through their work that the exact structure of the system ($SIR/SIRS/SEIR$) did not have much influence on the optimal solution. We tested this with our model, which becomes

$$\min_{\mathrm{u}} \quad J(u) = \int_0^T [AI_F(t) + cu_{jf}^2(t) + du_{sf}^2(t)] \quad dt, \tag{7.9}$$
$$u \in \{u_n : 0 \leq u_i \leq 2.3\}, n = jf, sf$$

subject to

$$\frac{\mathrm{d}J_F}{\mathrm{d}t} = \frac{j_F N_F}{\phi} + \alpha q(\alpha) P_F - (u_{jf}(t) + \eta_F + \frac{1}{\phi}) J_F, \tag{7.10a}$$
$$\frac{\mathrm{d}S_F}{\mathrm{d}t} = \frac{(1-j_F)N_F}{\phi} + \eta_F J_F - \lambda_F S_F + \sigma_F \gamma_F I_F - (u_{sf}(t) + \frac{1}{\phi}) S_F + (1 - q(\alpha))\alpha P_F + \epsilon_F R_F, \tag{7.10b}$$
$$\frac{\mathrm{d}P_F}{\mathrm{d}t} = u_{jf}(t) J_F + u_{sf}(t) S_F - (\alpha + \frac{1}{\phi}) P_F, \tag{7.10c}$$
$$\frac{\mathrm{d}I_F}{\mathrm{d}t} = \lambda_F S_F - (\gamma_F + \frac{1}{\phi}) I_F, \tag{7.10d}$$
$$\frac{\mathrm{d}R_F}{\mathrm{d}t} = (1 - \sigma_F)\gamma_F I_F - (\epsilon_F + \frac{1}{\phi}) R_F, \tag{7.10e}$$
$$\frac{\mathrm{d}J_M}{\mathrm{d}t} = \frac{j_m N_M}{\phi} - (\eta_M + \frac{1}{\phi}) J_M, \tag{7.10f}$$
$$\frac{\mathrm{d}S_M}{\mathrm{d}t} = \frac{(1-j_M)N_M}{\phi} + \eta_M J_M - \lambda_M S_M + \sigma_M \gamma_M I_M + \epsilon_M R_M - \frac{1}{\phi} S_M, \tag{7.10g}$$
$$\frac{\mathrm{d}I_M}{\mathrm{d}t} = \lambda_M S_M - (\gamma_M + \frac{1}{\phi}) I_M, \tag{7.10h}$$
$$\frac{\mathrm{d}R_M}{\mathrm{d}t} = (1 - \sigma_M)\gamma_M I_M - (\epsilon_M + \frac{1}{\phi}) R_M. \tag{7.10i}$$

The adjoint equations are

$$\lambda_1^{'} = (\eta_F + u_{jf}(t) + \frac{1}{\phi})\lambda_1 - \eta_F\lambda_2 - u_{jf}(t)\lambda_3 + \frac{z\beta S_M I_F}{(N_F - J_F)^2}\lambda_7 - \frac{z\beta S_M I_F}{(N_F - J_F)^2}\lambda_8, \tag{7.11a}$$

$$\lambda_2^{'} = (\frac{z\beta I_M}{N_M - J_M} + u_{sf}(t) + \frac{1}{\phi})\lambda_2 - u_{sf}(t)\lambda_3 - \frac{z\beta I_M}{N_M - J_M}\lambda_4, \tag{7.11b}$$

$$\lambda_3^{'} = -q(\alpha)\alpha\lambda_1 - (1 - q(\alpha))\alpha\lambda_2 + (\alpha + \frac{1}{\phi})\lambda_3, \tag{7.11c}$$

$$\lambda_4^{'} = -A - \sigma_F\gamma_F\lambda_2 + (\gamma_F + \frac{1}{\phi})\lambda_4 - (1 - \sigma_F)\gamma_F\lambda_5 + \frac{z\beta S_M}{N_F - J_F}\lambda_7 - \frac{z\beta S_M}{N_F - J_F}\lambda_8, \tag{7.11d}$$

$$\lambda_5^{'} = -\epsilon_F\lambda_2 + (\epsilon_F + \frac{1}{\phi})\lambda_5, \tag{7.11e}$$

$$\lambda_6^{'} = \frac{z\beta S_F I_M}{(N_M - J_M)^2}\lambda_2 - \frac{z\beta S_F I_M}{(N_M - J_M)^2}\lambda_4 + (\eta_M + \frac{1}{\phi})\lambda_6 - \eta_M\lambda_7, \tag{7.11f}$$

$$\lambda_7^{'} = (\frac{z\beta I_F}{N_F - J_F} + \frac{1}{\phi})\lambda_7 - \frac{z\beta I_F}{N_F - J_F}\lambda_8, \tag{7.11g}$$

$$\lambda_8^{'} = \frac{z\beta S_F}{N_M - J_M}\lambda_2 - \frac{z\beta S_F}{N_M - J_M}\lambda_4 - \sigma_M\gamma_M\lambda_7 + (\gamma_M + \frac{1}{\phi})\lambda_8 - (1 - \sigma_M)\gamma_M\lambda_9, \tag{7.11h}$$

$$\lambda_9^{'} = -\epsilon_M\lambda_7 + (\epsilon_M + \frac{1}{\phi})\lambda_9, \tag{7.11i}$$

with transversality conditions $\lambda_r(T) = 0$ ($r = 1, ..., 9$, T is the end time). The optimal functions are as previously;

$$u_{jf}^*(t) = \frac{(\lambda_1 - \lambda_3)J_F}{2c},$$

and

$$u_{sf}^*(t) = \frac{(\lambda_2 - \lambda_3)S_F}{2d}.$$

In taking $\sigma_i = 0.5$ and $\epsilon_i = 0.2$, we find the class profiles and optimal functions as in Figure 7-7. The results are qualitatively very similar to those found in the case without natural immunity, with a larger proportion of sexually active individuals vaccinated. Quantitatively, Figure 7-7 shows higher initial rates of vaccination than Figure 7-2.

7.5 Conclusions

There are several conclusions that we can draw from this study. Firstly we found that, provided the vaccine is still effective when individuals become sexually active, the optimal solution consists of vaccinating both sexually active and non-sexually active

females, with sexually active females vaccinated at a higher rate, after which point vaccination levels can be reduced (Figure 7-2). This suggests that vaccination must continue, even at low levels, for as long as we wish to control the disease.

We found that the vaccination of sexually active individuals has a greater impact on the optimal solution than the vaccination of non-sexually active individuals (Figure 7-3). The function $u_{sf}(t)$ barely changes, whether $u_{jf}(t) \equiv 0$ or not, but when $u_{sf}(t) \equiv 0$, $u_{jf}(t)$ must be maintained at a higher level (compared to Figure 7-2) for most of the time period. This result highlights the importance of including a catch-up programme in HPV vaccination policy if the disease is to be controlled.

We found that the relative cost of the control on the sexually active female class influenced the behaviour of the control on the non-sexually active female class (Figure 7-4). The difference in $u_{jf}(t)$ as the cost on $u_{sf}(t)$ increased is quite pronounced; as the cost of $u_{sf}(t)$ increased, $u_{jf}(t)$ was maintained at a much higher level for longer, to make up for the deficit caused by the absence of $u_{sf}(t)$.

The importance of considering an optimal control problem was highlighted in Figure 7-5 where very different levels of protection were shown to have the same effect. This highlights a benefit of using optimal control - the control is able to adapt over time, unlike a constant level of control.

The results presented in Figure 7-6 imply that it is cost-effective to vaccinate males as well as females, even when there is no cost associated with male infection. We have not considered the possible role of HPV in other genital cancers here, although any added cost on the male infection would be likely to increase the case for including them in a vaccination strategy.

Finally, Figure 7-7 shows that the inclusion of temporary natural immunity does not significantly affect the optimal functions. This result supports [50], which found that the form of the model system did not greatly influence the optimal solution.

The use of optimal control in assessing the cost-effectiveness of the HPV vaccine has not previously been attempted. Cost-effectiveness studies have been done using techniques such as decision analysis, with a variety of results [11, 39, 10]. Our results differ with the majority of other studies in that we suggest that vaccination of males would be cost-effective and that the catch-up programme (vaccinating older individuals) plays a large role in controlling the disease. Of the other studies done, the conclusions have mainly been that male vaccination would not be cost-effective, or would only be cost-effective in specific situations. The role of the catch-up programme was generally considered cost-effective, although [39] concluded that, if it was a choice of vaccinating a greater number of 12 year olds or 18 year olds, it was more cost-effective to vaccinate 12 year olds.

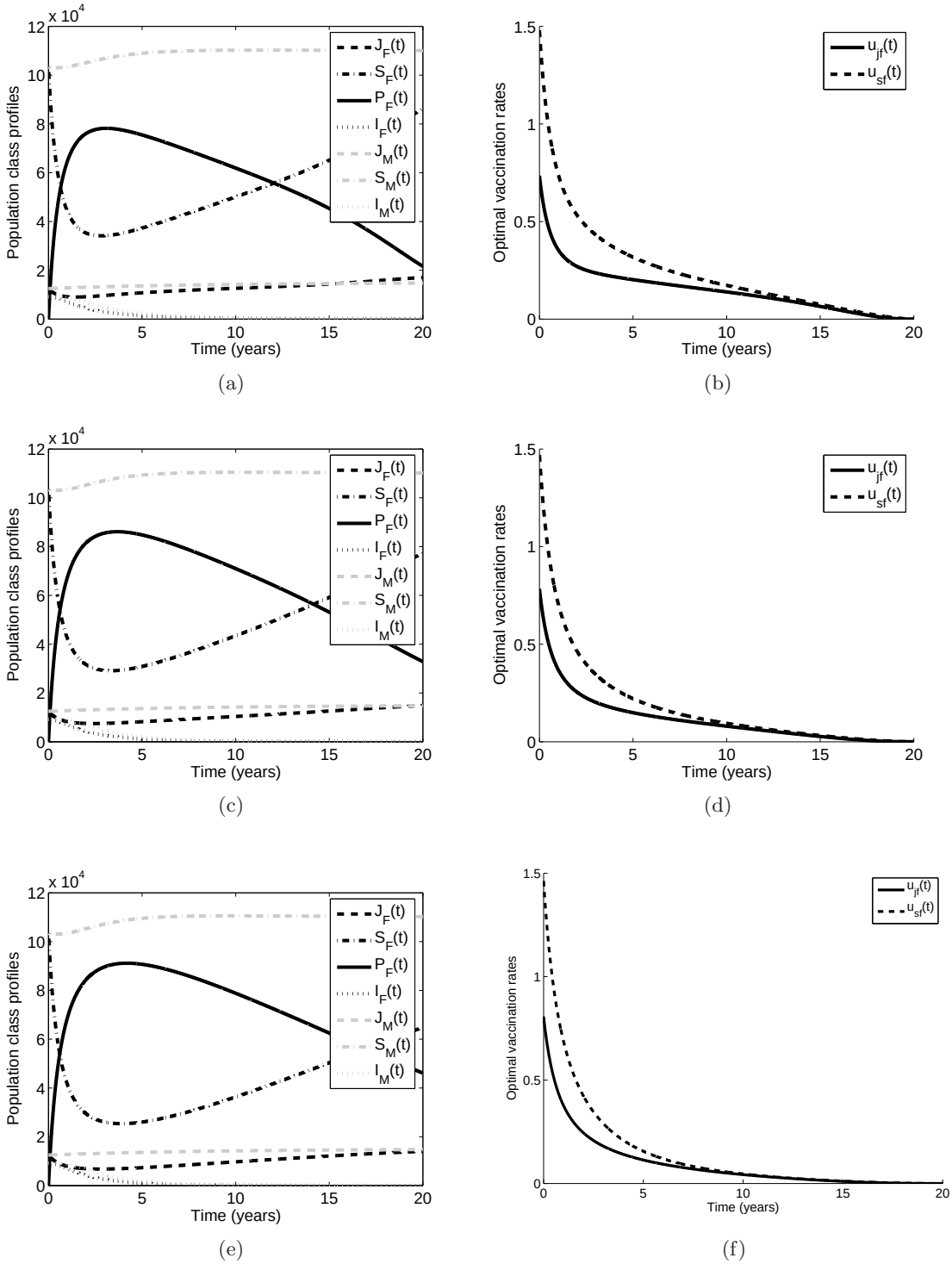


Figure 7-2: The time profiles and the optimal control functions for a parameter set, initial conditions and weightings as detailed in the methods and in Table 3.2. Figures 7-2a and 7-2b show the case when $\alpha = 0.2$, Figures 7-2c and 7-2d have $\alpha = 0.1$ and Figures 7-2e and 7-2f have $\alpha = 0.05$.

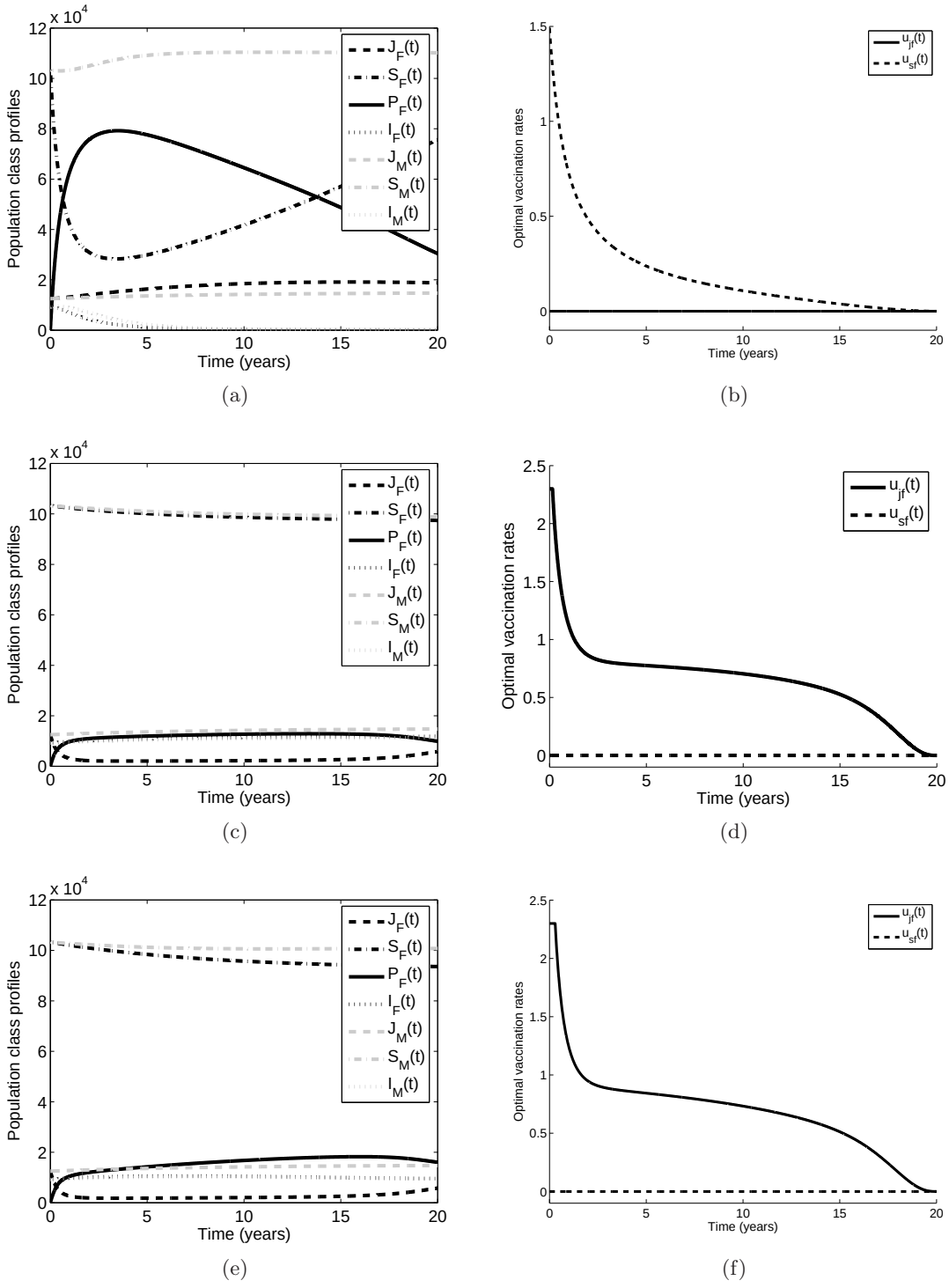


Figure 7-3: Time profiles and optimal vaccination strategies when one of the controls is removed. Figures 7-3a and 7-3b show the result with $u_{jf}(t) = 0$; 7-3c and 7-3d with $u_{sf}(t) = 0$. All of these figures have $\alpha = 0.1$. Figures 7-3e and 7-3f show the result with $u_{sf}(t) = 0$ and $\alpha = 0.05$. In all cases $T = 20$.

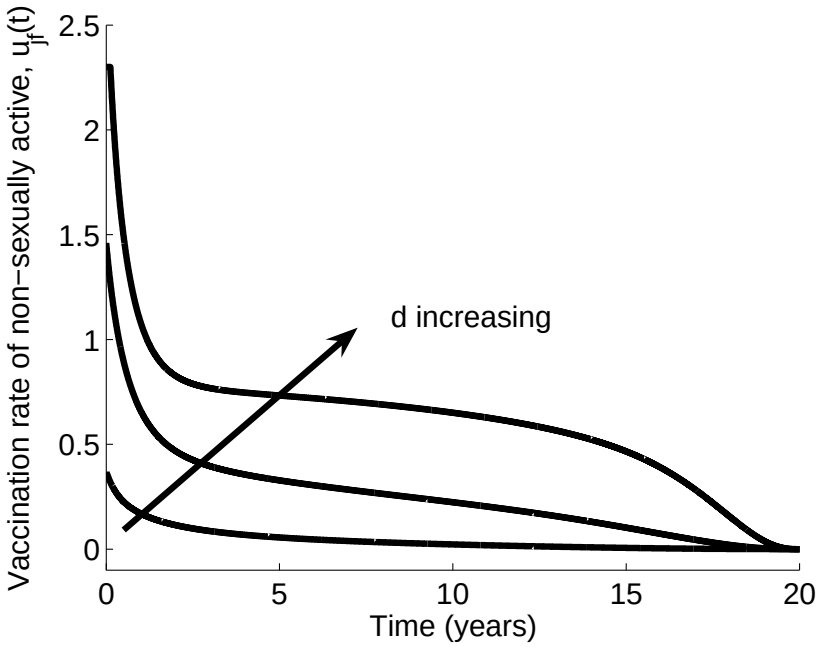


Figure 7-4: A graph of the control $u_{jf}(t)$ as d varies. Note that the smaller the value of d, the quicker the control tends to 0. For the largest vales of d, the control only approaches zero near the end time. d is set at 0.1, 10 and 1000, with A and c as given above. The parameter set and initial conditions are as for Figure 7-2c.

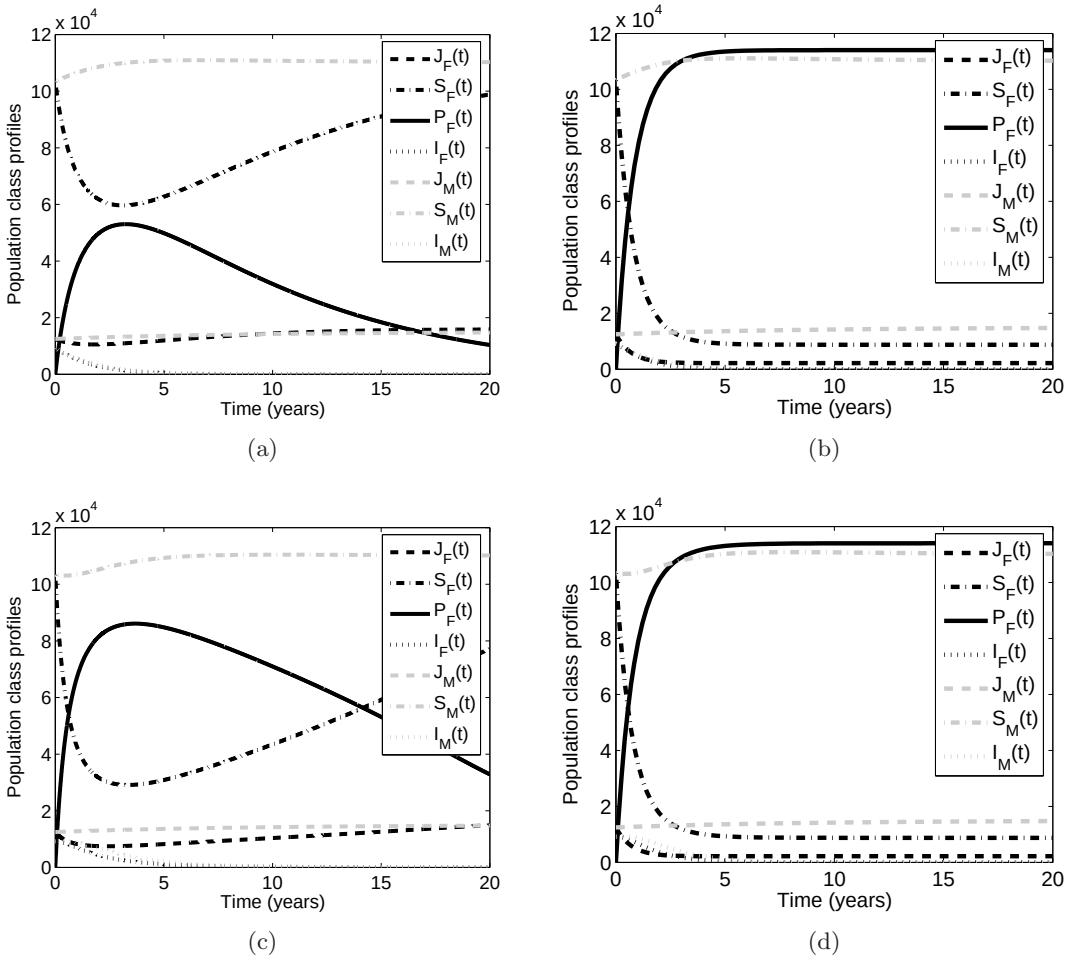
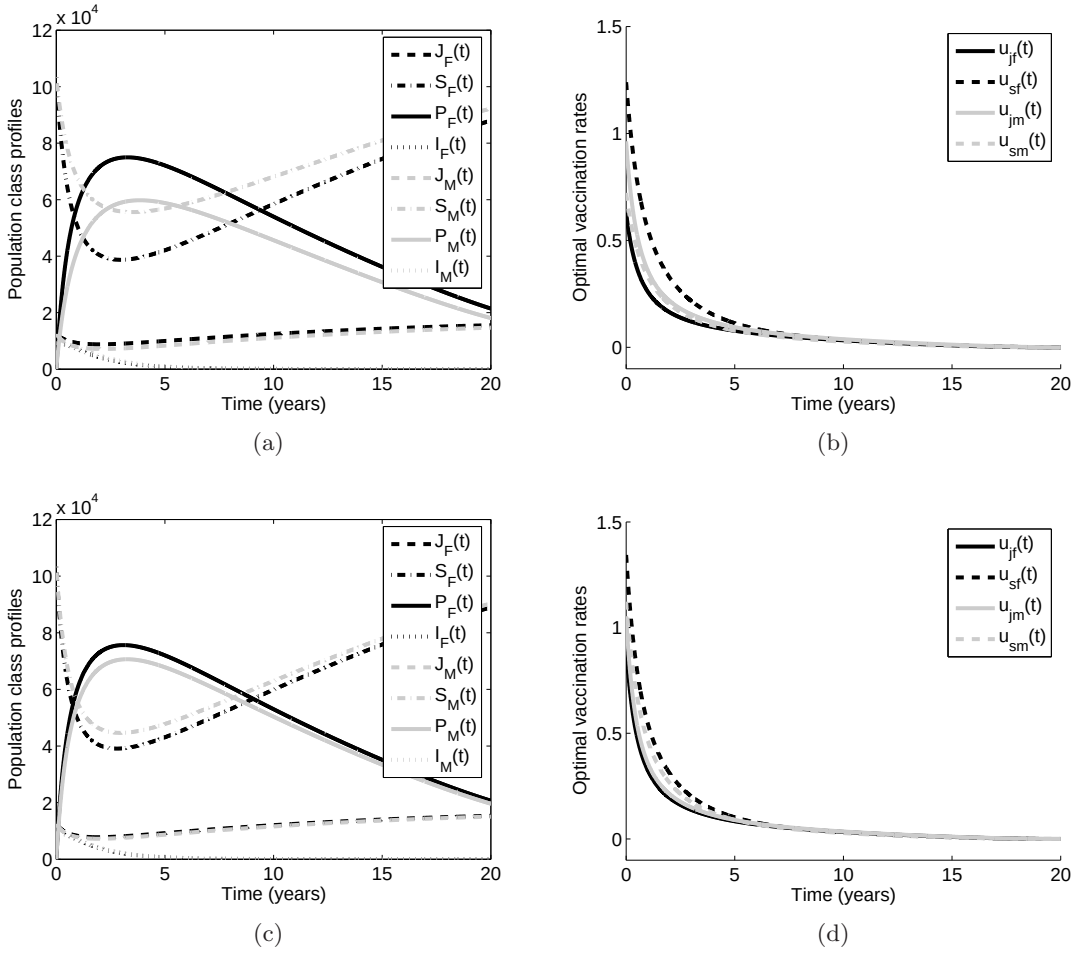


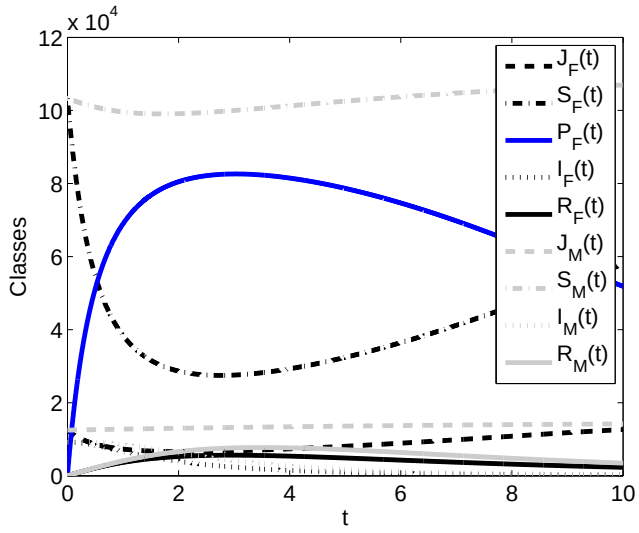
Figure 7-5: A comparison of the class profiles from the optimal control and constant control models, using the same set of parameter values and initial conditions in each case. Figures 7-5a and 7-5b show the time profiles for the optimal control and constant control cases respectively with $z = 1$. Figures 7-5c and 7-5d again show the time profiles for the optimal control and constant control cases respectively, but now with $z = 2$.



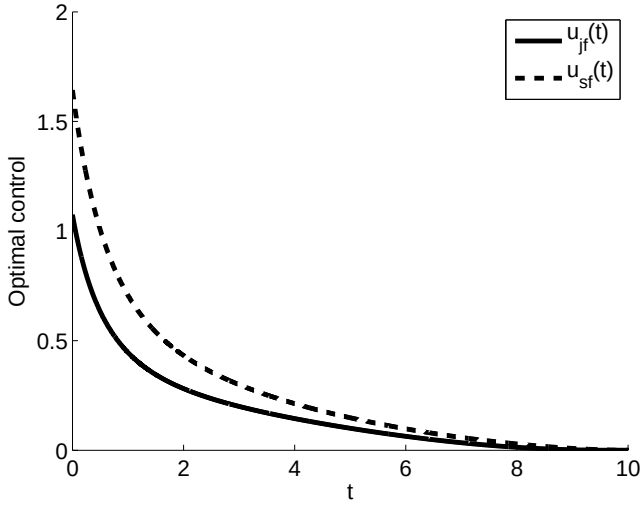
(a) (b)

(c) (d)

Figure 7-6: Inclusion of male vaccination. The class profiles and the optimal control functions for a parameter set, initial conditions and weightings as detailed in the methods and in Table 3.2. In Figures 7-6a and 7-6b, weighting on male infection is $B = 0$. In Figures 7-6c and 7-6d, weighting on male infection is $B = 0.0001$. Initial conditions were $J_i(0) = 12500$, $S_i(0) = 103325$, $P_i(0) = 0$, $I_i(0) = 9175$.



(a)



(b)

Figure 7-7: The class profiles and optimal functions when natural immunity is included. We set $\sigma_i = 0.5$ and $\epsilon_i = 0.2$. All other parameters and initial conditions are as described in the text and Table 3.2.

Chapter 8

Optimal Control applied to an Age-dependent Model

We can develop the work presented in the previous chapter on optimal control by applying optimal control to an age-dependent ODE. We follow Pontryagin's Maximum Principle, as before, and characterise the optimal control. We are now interested in establishing at what ages vaccination should take place. The vaccination strategy for the HPV vaccine is unique in the UK [4]; using optimal control to assess the age-dependent problem can show us whether this strategy is justified. Although this has been considered in previous cost-effectiveness studies [12, 22, 37], we are using optimal control to attempt to answer this question.

8.1 Model

We apply optimal control to the age-dependent ODE model in the same way as we applied it to the time-dependent ODE in the previous chapter; the schematic of this system can be seen in Figure 8-1.

We use a non-integral force of infection that assumes contact only occurs between individuals of the same age [31],

$$\lambda_i(a) = z_i(a)\beta\frac{I_k(a)}{N_k(a) - J_k(a)}. \tag{8.1}$$

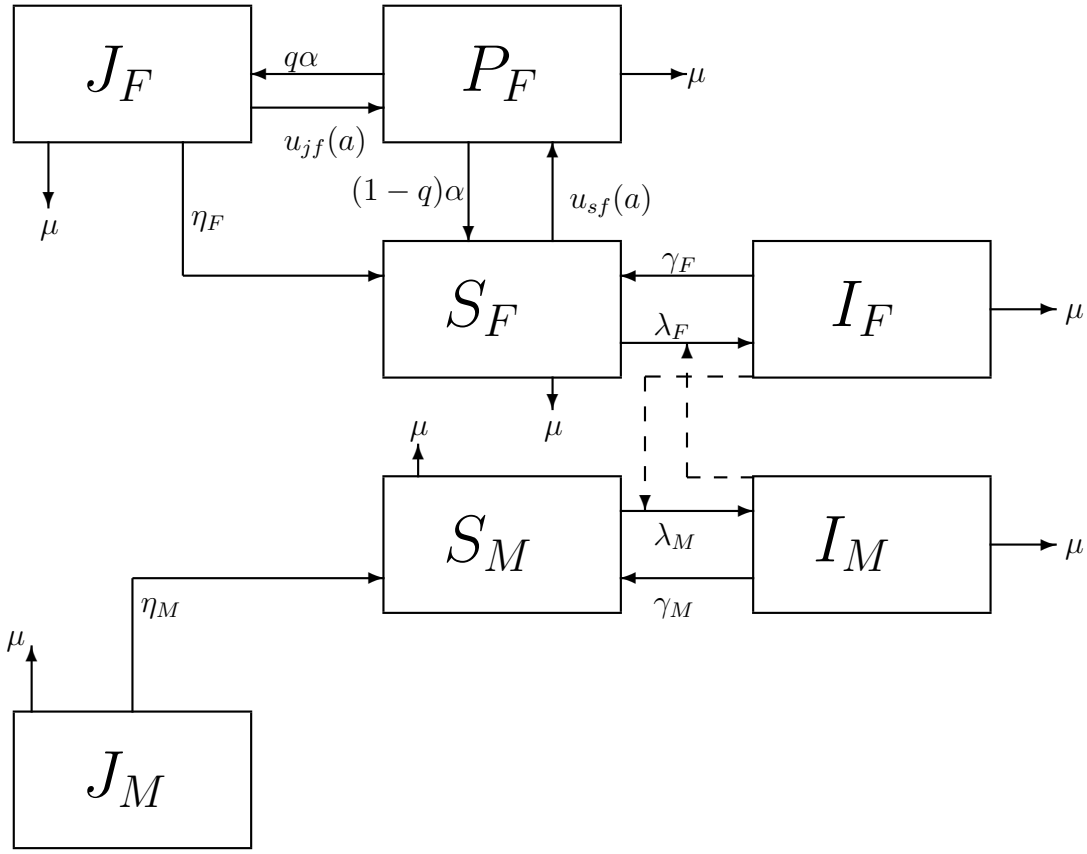


Figure 8-1: Schematic of the model system.

The system (from Figure 8-1) is

$$\frac{\mathrm{d}J_F}{\mathrm{d}a} = -(\eta_F(a) + \mu_F(a) + u_{jf}(a))J_F + q(\alpha)\alpha(a)P_F, \tag{8.2a}$$
$$\frac{\mathrm{d}S_F}{\mathrm{d}a} = -(\lambda(a) + \mu_F(a) + u_{sf}(a))S_F + (1 - q(\alpha))\alpha(a)P_F + \eta_F(a)J_F + \gamma_F I_F, \tag{8.2b}$$
$$\frac{\mathrm{d}P_F}{\mathrm{d}a} = -(\alpha(a) + \mu_F(a))P_F + u_{jf}(a)J_F + u_{sf}(a)S_F, \tag{8.2c}$$
$$\frac{\mathrm{d}I_F}{\mathrm{d}a} = -(\gamma_F + \mu_F(a))I_F + \lambda_F(a)S_F, \tag{8.2d}$$
$$\frac{\mathrm{d}J_M}{\mathrm{d}a} = -(\eta_M(a) + \mu_M(a))J_M, \tag{8.2e}$$
$$\frac{\mathrm{d}S_M}{\mathrm{d}a} = -(\lambda_M(a) + \mu_M(a))S_M + \eta_M(a)J_M + \gamma_M I_M, \tag{8.2f}$$
$$\frac{\mathrm{d}I_M}{\mathrm{d}a} = -(\gamma_M + \mu_M(a))I_M + \lambda_M(a)S_M, \tag{8.2g}$$
$$\frac{\mathrm{d}N_F}{\mathrm{d}a} = -\mu_F(a)N_F, \tag{8.2h}$$
$$\frac{\mathrm{d}N_M}{\mathrm{d}a} = -\mu_M(a)N_M. \tag{8.2i}$$

8.2 Adding Optimal Control

We add optimal control to the model in the same way as in Chapter 7. Our two controls are $u_{jf}(a)$ and $u_{sf}(a)$, which represent the proportion of either the $J_F(a)$ or $S_F(a)$ class (respectively) that is vaccinated for each age. We set the objective functional to be

$$\min_{\mathrm{u}} \quad J(u) = \int_{a_0}^{a_{max}} [AI_F(a) + cu_{jf}^2(a) + du_{sf}^2(a)] \quad \mathrm{d}a, \tag{8.3}$$
$$u \in \{u_n : 0 \leq u_n \leq 2.3\}, n = jf, sf$$

subject to the underlying infection dynamics. As in Chapter 7, we need to define the Hamiltonian and adjoint equations, and so characterise the optimal control. The

Hamiltonian is

$$H = AI_F + cu_{jf}^2 + du_{sf}^2 + \lambda_1(-(\eta_F(a) + \mu_F(a) + u_{jf}(a))J_F + q(\alpha)\alpha(a)P_F)$$
$$+ \lambda_2(\eta_F(a)J_F - \frac{z_F(a)\beta S_F I_M}{N_M - J_M} + \gamma_F I_F - (u_{sf}(a) + \mu_F(a))S_F + (1 - q(\alpha))\alpha(a)P_F)$$
$$+ \lambda_3(u_{jf}(a)J_F + u_{sf}(a)S_F - (\alpha(a) + \mu_F(a))P_F) + \lambda_4(\frac{z_F(a)\beta S_F I_M}{N_M - J_M} - (\gamma_F + \mu_F(a))I_F)$$
$$+ \lambda_5(-(\eta_M(a) + \mu_M(a))J_M) + \lambda_6(\eta_M(a)J_M - \frac{z_M(a)\beta S_M I_F}{N_F - J_F} + \gamma_M I_M - \mu_M(a)S_M)$$
$$+ \lambda_7(\frac{z_M(a)\beta S_M I_F}{N_F - J_F} - (\gamma_M + \mu_M(a))I_M) + \lambda_8(-\mu_F(a)N_F) + \lambda_9(-\mu_M(a)N_M),$$

with the adjoint equations as

$$\lambda_1^{'} = (\eta_F(a) + \mu_F(a) + u_{jf}(a))\lambda_1 - \eta_F(a)\lambda_2 - u_{jf}(a)\lambda_3 + \frac{z_M(a)\beta S_M I_F}{(N_F - J_F)^2}\lambda_6 - \frac{z_M(a)\beta S_M I_F}{(N_F - J_F)^2}\lambda_7, \tag{8.4a}$$

$$\lambda_2^{'} = (\frac{z_F(a)\beta I_M}{N_M - J_M} + u_{sf}(a) + \mu_F(a))\lambda_2 - u_{sf}(a)\lambda_3 - \frac{z_F(a)\beta I_M}{N_M - J_M}\lambda_4, \tag{8.4b}$$

$$\lambda_3^{'} = -q(\alpha)\alpha(a)\lambda_1 - (1 - q(\alpha))\alpha(a)\lambda_2 + (\alpha(a) + \mu_F(a))\lambda_3, \tag{8.4c}$$

$$\lambda_4^{'} = -A - \gamma_F\lambda_2 + (\gamma_F + \mu_F(a))\lambda_4 + \frac{z_M(a)\beta S_M}{N_F - J_F}\lambda_6 - \frac{z_M(a)\beta S_M}{N_F - J_F}\lambda_7, \tag{8.4d}$$

$$\lambda_5^{'} = \frac{z_F(a)\beta S_F I_M}{(N_M - J_M)^2}\lambda_2 - \frac{z_F(a)\beta S_F I_M}{(N_M - J_M)^2}\lambda_4 + (\eta_M(a) + \mu_M(a))\lambda_5 - \eta_M(a)\lambda_6, \tag{8.4e}$$

$$\lambda_6^{'} = (\frac{z_M(a)\beta I_F}{N_F - J_F} + \mu_M(a))\lambda_6 - \frac{z_M(a)\beta I_F}{N_F - J_F}\lambda_7, \tag{8.4f}$$

$$\lambda_7^{'} = \frac{z_F(a)\beta S_F}{N_M - J_M}\lambda_2 - \frac{z_F(a)\beta S_F}{N_M - J_M}\lambda_4 - \gamma_M\lambda_6 + (\gamma_M + \mu_M(a))\lambda_7, \tag{8.4g}$$

$$\lambda_8{}' = \frac{-z_M(a)\beta I_F S_M}{(N_F - J_F)^2}\lambda_6 + \frac{z_M(a)\beta I_F S_M}{(N_F - J_F)^2}\lambda_7 + \mu_F(a)\lambda_8, \tag{8.4h}$$

$$\lambda_9{}' = \frac{-z_F(a)\beta I_M S_F}{(N_M - J_M)^2}\lambda_2 + \frac{z_F(a)\beta I_M S_F}{(N_M - J_M)^2}\lambda_4 + \mu_M(a)\lambda_9. \tag{8.4i}$$

The transversality conditions are $\lambda_v(a_{max}) = 0$ ($v = 1, ..., 9$, a_{max} is the end age). Finally, the characterisation of the optimal control functions is

$$u_{jf}^*(a) = \frac{(\lambda_1 - \lambda_3)J_F}{2c},$$

and

$$u_{sf}^*(a) = \frac{(\lambda_2 - \lambda_3)S_F}{2d}.$$

This optimal control problem can be compared to a constant control model, where $u_{jf}(a) = u_{sf}(a) = p$, a constant. We consider this model in our numerical solutions and compare the results.

8.2.1 Including Male Vaccination

We extend (8.2) by including male vaccination in our model. As in Chapter 7, we introduce two controls on the male classes, $u_{jm}(a)$ and $u_{sm}(a)$, which are included for males in the same way as the controls described above in the female-only vaccination scenario. The weighting on male infection is B, with $B = 0$ or $B = 0.0001$ in the numerical solutions. The problem with a male vaccinated class is as follows:

$$\min_{\mathrm{u}} \quad J(u) = \int_{a_0}^{a_{max}} [AI_F(a) + BI_M(a) + c(u_{jf}^2(a) + u_{jm}^2(a)) + d(u_{sf}^2(a) + u_{sm}^2(a))] \quad \mathrm{d}a,$$
$$u \in \{u_n : 0 \leq u_n \leq 2.3\}, n = jf, sf$$

subject to

$$\frac{\mathrm{d}J_F}{\mathrm{d}a} = -(u_{jf}(a) + \eta_F(a) + \mu_F(a))J_F + \alpha(a)q(\alpha)P_F, \tag{8.5a}$$
$$\frac{\mathrm{d}S_F}{\mathrm{d}a} = \eta_F(a)J_F - \lambda_F S_F + \gamma_F I_F - (u_{sf}(a) + \mu_F(a))S_F + (1 - q(\alpha))\alpha(a)P_F, \tag{8.5b}$$
$$\frac{\mathrm{d}P_F}{\mathrm{d}a} = u_{jf}(a)J_F + u_{sf}(a)S_F - (\alpha(a) + \mu_F(a))P_F, \tag{8.5c}$$
$$\frac{\mathrm{d}I_F}{\mathrm{d}a} = \lambda_F S_F - (\gamma_F + \mu_F(a))I_F, \tag{8.5d}$$
$$\frac{\mathrm{d}J_M}{\mathrm{d}a} = -(u_{jm}(a) + \eta_M(a) + \mu_M(a))J_M + \alpha(a)q(\alpha)P_M, \tag{8.5e}$$
$$\frac{\mathrm{d}S_M}{\mathrm{d}a} = \eta_M(a)J_M - \lambda_M S_M + \gamma_M I_M - (u_{sm}(a) + \mu_M(a))S_M + (1 - q(\alpha))\alpha(a)P_M, \tag{8.5f}$$
$$\frac{\mathrm{d}P_M}{\mathrm{d}a} = u_{jm}(a)J_M + u_{sm}(a)S_M - (\alpha(a) + \mu_M(a))P_M, \tag{8.5g}$$
$$\frac{\mathrm{d}I_M}{\mathrm{d}a} = \lambda_M S_M - (\gamma_M + \mu_M(a))I_M, \tag{8.5h}$$
$$\frac{\mathrm{d}N_F}{\mathrm{d}a} = -\mu_F(a)N_F, \tag{8.5i}$$
$$\frac{\mathrm{d}N_M}{\mathrm{d}a} = -\mu_M(a)N_M. \tag{8.5j}$$

We can generate the Hamiltonian, adjoint equations and characterise the optimal

control as before; the adjoint equations are

$$\lambda_1^{'} = (\eta_F(a) + u_{jf}(a) + \mu_F(a))\lambda_1 - \eta_F(a)\lambda_2 - u_{jf}(a)\lambda_3 + \frac{z_M(a)\beta S_M I_F}{(N_F - J_F)^2}\lambda_6 - \frac{z_M(a)\beta S_M I_F}{(N_F - J_F)^2}\lambda_8, \tag{8.6a}$$

$$\lambda_2^{'} = (\frac{z_F(a)\beta I_M}{N_M - J_M} + u_{sf}(a) + \mu_F(a))\lambda_2 - u_{sf}(a)\lambda_3 - \frac{z_F(a)\beta I_M}{N_M - J_M}\lambda_4, \tag{8.6b}$$

$$\lambda_3^{'} = -q(\alpha)\alpha(a)\lambda_1 - (1 - q(\alpha))\alpha(a)\lambda_2 + (\alpha(a) + \mu_F(a))\lambda_3, \tag{8.6c}$$

$$\lambda_4^{'} = -A - \gamma_F\lambda_2 + (\gamma_F + \mu_F(a))\lambda_4 + \frac{z_M(a)\beta S_M}{N_F - J_F}\lambda_6 - \frac{z_M(a)\beta S_M}{N_F - J_F}\lambda_8, \tag{8.6d}$$

$$\lambda_5^{'} = (\eta_M(a) + u_{jm}(a) + \mu_M(a))\lambda_5 - \eta_M(a)\lambda_6 - u_{jm}(a)\lambda_7 + \frac{z_F(a)\beta S_F I_M}{(N_M - J_M)^2}\lambda_2 - \frac{z_F(a)\beta S_F I_M}{(N_M - J_M)^2}\lambda_4, \tag{8.6e}$$

$$\lambda_6^{'} = (\frac{z_M(a)\beta I_F}{N_F - J_F} + u_{sm}(a) + \mu_M(a))\lambda_6 - u_{sm}(a)\lambda_7 - \frac{z_M(a)\beta I_F}{N_F - J_F}\lambda_8, \tag{8.6f}$$

$$\lambda_7^{'} = -q(\alpha)\alpha(a)\lambda_5 - (1 - q(\alpha))\alpha(a)\lambda_6 + (\alpha(a) + \mu_M(a))\lambda_7, \tag{8.6g}$$

$$\lambda_8^{'} = -B - \gamma_M\lambda_6 + (\gamma_M + \mu_M(a))\lambda_8 + \frac{z_F(a)\beta S_F}{N_M - J_M}\lambda_2 - \frac{z_M(a)\beta S_M}{N_M - J_M}\lambda_4, \tag{8.6h}$$

$$\lambda_9{}' = \frac{-z_M(a)\beta I_F S_M}{(N_F - J_F)^2}\lambda_6 + \frac{z_M(a)\beta I_F S_M}{(N_F - J_F)^2}\lambda_8 + \mu_F(a)\lambda_9, \tag{8.6i}$$

$$\lambda_{10}{}' = \frac{-z_F(a)\beta I_M S_F}{(N_M - J_M)^2}\lambda_2 + \frac{z_F(a)\beta I_M S_F}{(N_M - J_M)^2}\lambda_4 + \mu_M(a)\lambda_{10}, \tag{8.6j}$$

with transversality conditions $\lambda_g(T) = 0$ ($g = 1, ..., 10$, T is end time). The female optimal control functions are characterised as

$$u_{jf}^*(a) = \frac{(\lambda_1 - \lambda_3)J_F}{2c},$$

and

$$u_{sf}^*(a) = \frac{(\lambda_2 - \lambda_3)S_F}{2d}.$$

The male controls are

$$u_{jm}^*(a) = \frac{(\lambda_5 - \lambda_7)J_F}{2c},$$

and

$$u_{sm}^*(a) = \frac{(\lambda_6 - \lambda_7)S_F}{2d}.$$

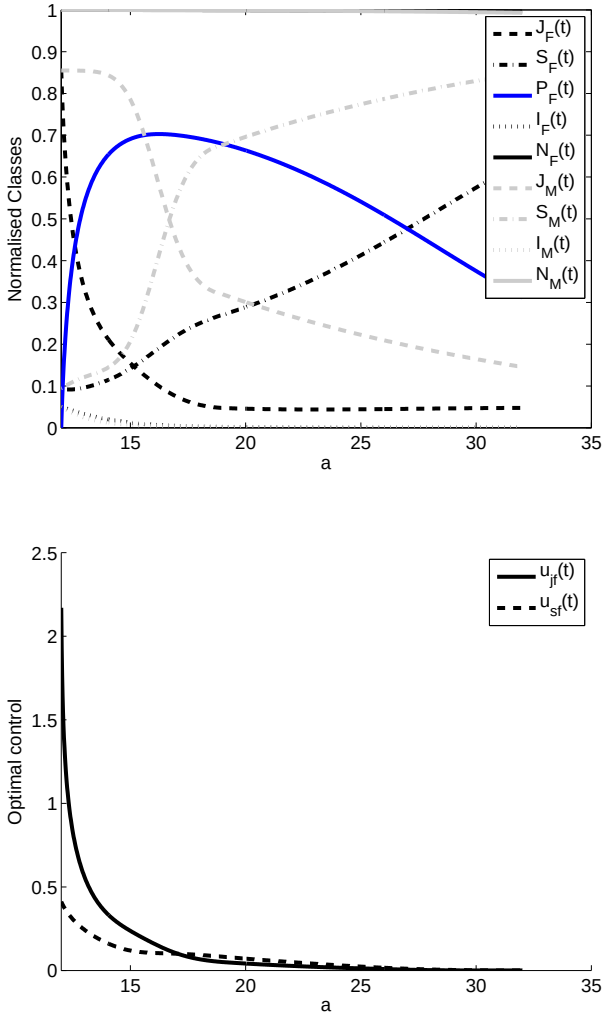
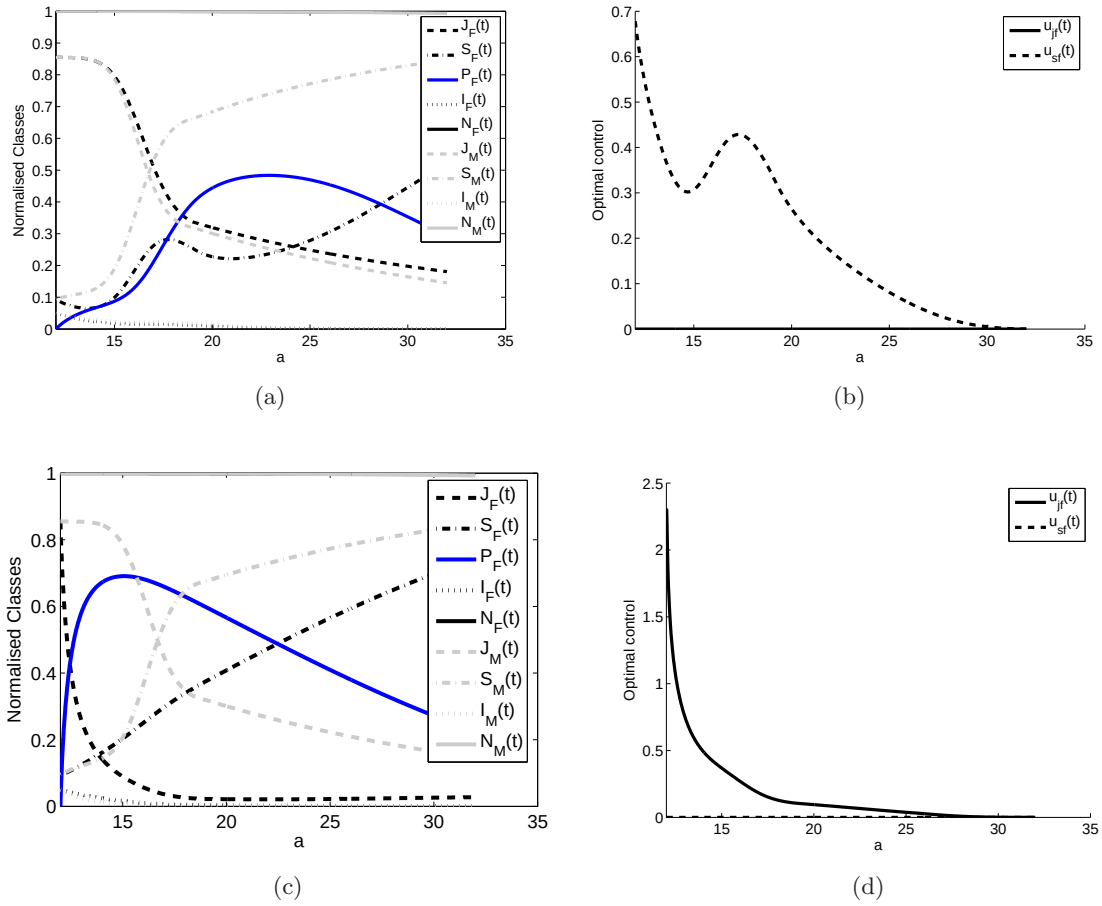


Figure 8-2: The class profiles and control functions for the age-dependent ODE.

8.3 Numerical Solutions

In the following numerical solutions, the initial conditions are $P_i(a_0) = 0$, $J_i(a_0) = 0.855N_i(a_0)$, $I_i(a_0) = 0.05N_i(a_0)$ and $S_i(a_0) = 0.095N_i(a_0)$, with $N_i(a_0) = 125,000$. The graphs are then scaled to show the proportion of the population in each class. We run the model between the ages 12 and 32. We use age-dependent parameters as described in Chapter 3 and set $\gamma_i = 1$. The weightings used for the objective functional are $A = 0.0002$, $c = 0.1$ and $d = 1$ as in Chapter 7. Solving the optimal control problem given in Section 8.2 gives the Figures shown in 8-2.

The graph shows high levels of vaccination for non-sexually active females from the



(a) (b)

(c) (d)

Figure 8-3: Age profiles and optimal vaccination strategies when one of the controls is removed. Figures 8-3a and 8-3b show the result with $u_{jf}(a) = 0$. Figures 8-3c and 8-3d show the result with $u_{sf}(a) = 0$.

age of 12, with much lower levels of vaccination for the sexually active. As age increases, vaccination decreases sharply and the vaccination of sexually active individuals becomes more important, albeit at very low levels.

As in Chapter 7, we now extend our numerical solutions to consider a range of different scenarios. Firstly, we consider the impact of setting one of the controls to zero. This gives the graphs shown in Figure 8-3.

Unlike for the optimal control problem in Chapter 7, the control on the non-sexually active females, $u_{jf}(a)$, does not change significantly if $u_{sf}(a) \equiv 0$. When $u_{jf}(a) \equiv 0$, the control on $u_{sf}(a)$ initially decreases, as when $u_{jf}(a) \neq 0$, but is altered by an increase in vaccination that starts at $a \approx 15$, reaching a peak at $a \approx 17.5$, before decreasing again.

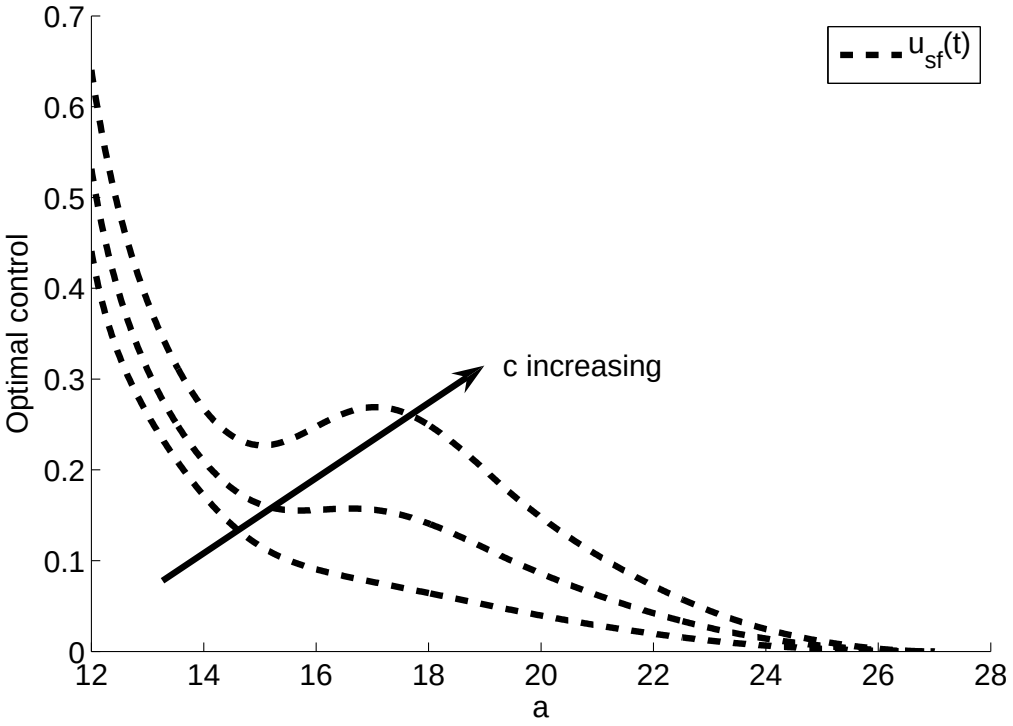


Figure 8-4: A graph of the control $u_{sf}(a)$ as c varies. The value of c is set at 0.01, 1 and 10, with A and d as given above. The parameter set and initial conditions are as given at the beginning of the section.

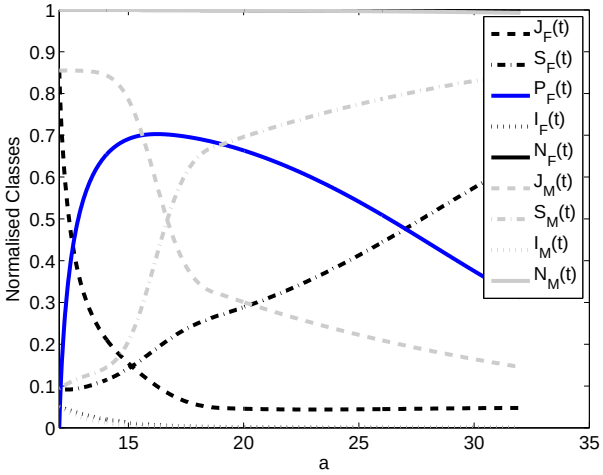
We found that, unlike in the time-dependent case, varying the value of d did not have a strong effect on $u_{jf}(a)$. However, varying c led to a significant change in $u_{sf}(a)$, as can be seen in Figure 8-4. This shows that, for $c \geq d$, the control $u_{sf}(a)$ decreases initially, then increases to a peak at $15 \leq a \leq 20$, before decreasing again.

8.3.1 Constant Control

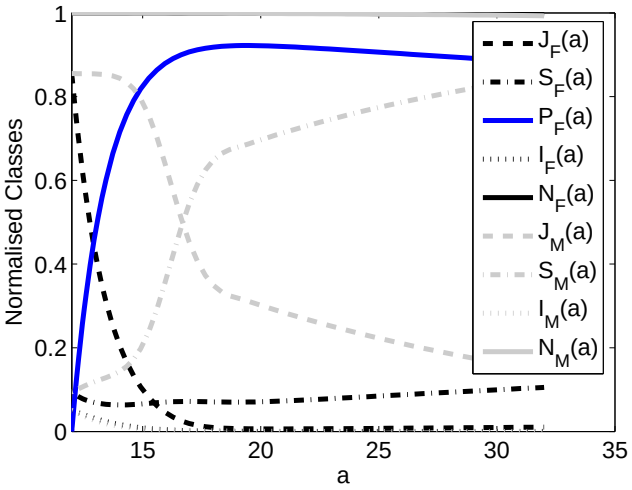
We compare the optimal solution to a constant control solution in Figure 8-5, where $u_n = p$, a constant. We see that infection is eradicated in either case, but the level of vaccination is much higher in the constant control situation (and therefore the expense is greater in this case).

8.3.2 Including Male Vaccination

We now include male vaccination in our model, by including a male protected class in the same way that the female protected class is included. The system and adjoint equa-



(a)



(b)

Figure 8-5: The class profiles for the age-dependent optimal (8-5a) and constant (8-5b) control problems. The constant rate of vaccination is $p = 0.7$.

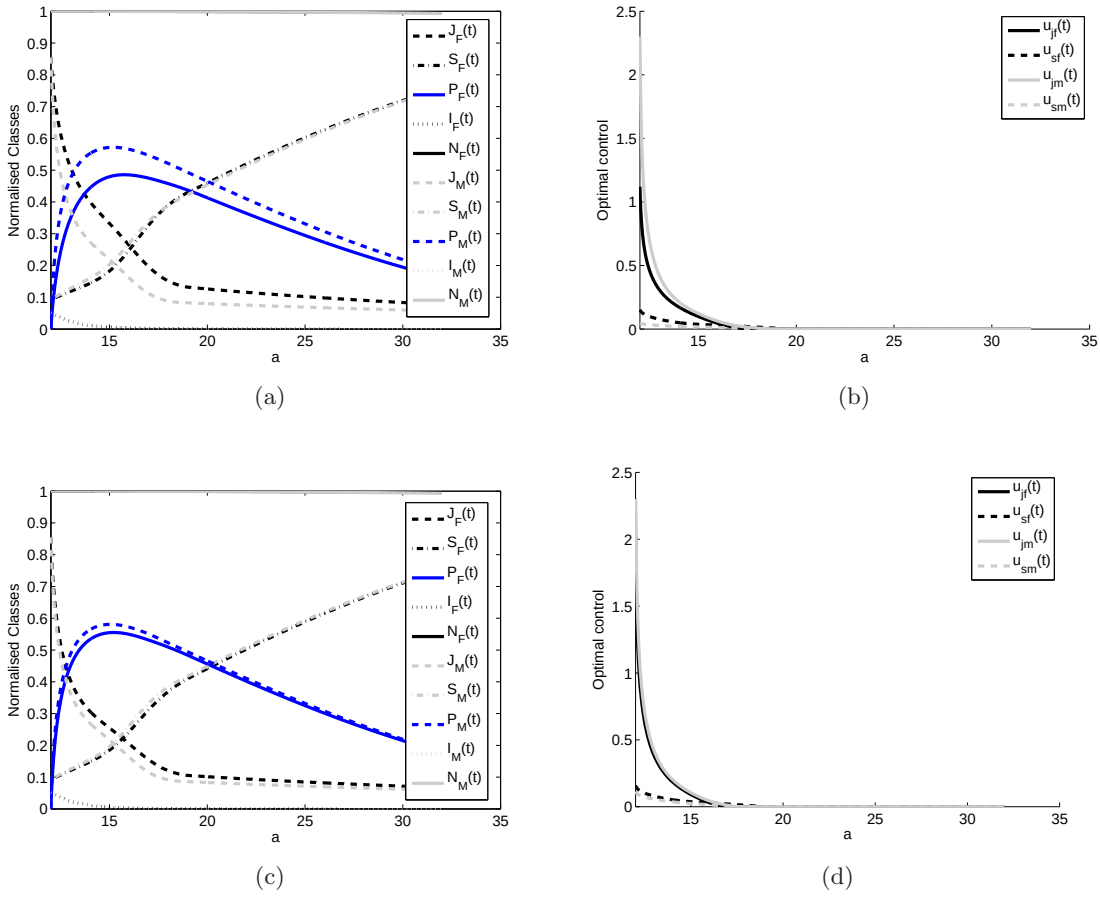
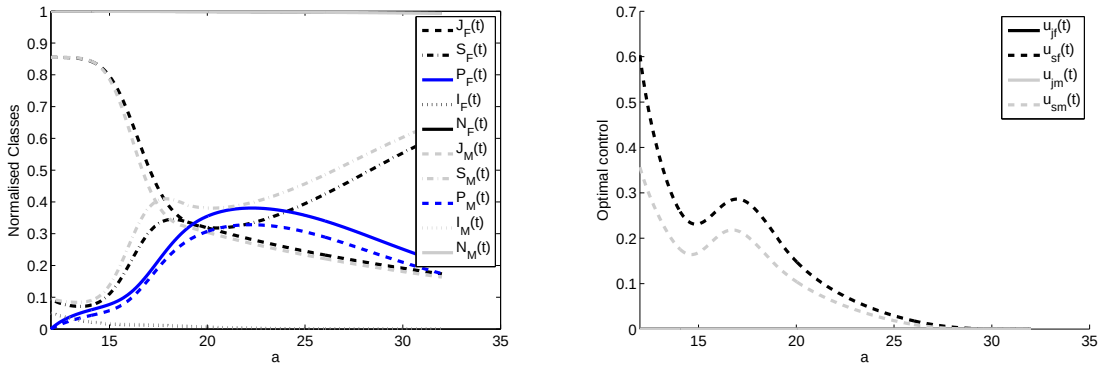


Figure 8-6: Inclusion of male vaccination. The class profiles and the optimal control functions for a parameter set, initial conditions and weightings as detailed in the methods and in Table 3.2. In Figures 8-6a and 8-6b, weighting on male infection is $B = 0$. In Figures 8-6c and 8-6d, weighting on male infection is $B = 0.0001$.

tions, and control functions, are given above. We now consider four control functions, two pertaining to the female-only vaccination strategy and two pertaining to the male vaccination strategy. As in Chapter 7, we consider two cases - firstly, when there is no cost associated to male vaccination (so weighting on the males $B = 0$), and when there is some cost ($B = 0.0001$). This presents the solutions given in Figure 8-6. We see that the solutions suggest it is cost-effective to vaccinate both males and females and there is a clear difference in the proportion of protected females to protected males.

We now consider $u_{jf}(a) = u_{jm}(a) = 0$ and the effect that this has on the remaining controls. Interestingly, we find that the functions are very similar to the case for female-only vaccination when $u_{jf}(a) = 0$, but that, unlike in Figure 8-6, more vaccination is indicated for the females rather than the males. The variation between the protected



(a) (b)

Figure 8-7: Inclusion of male vaccination when when $u_{jf}(a) = u_{jm}(a) = 0$ and $B = 0$. The class profiles and the optimal control functions for a parameter set, initial conditions and weightings as detailed in the methods and in Table 3.2.

classes in Figures 8-6 and 8-7 is not unexpected - in both cases we see a higher proportion of sexually active females vaccinated than sexually active males. This is in contrast to vaccination of non-sexually active males, which occurs at a higher rate than vaccination of non-sexually active females. The removal of vaccination of non-sexually active individuals therefore leads to a greater number of protected females than protected males.

8.4 Extending the Optimal Control Problem to a PDE Model

It is possible to build an optimal control problem based on a PDE model. We created a PDE system based on the schematic shown above (Figure 8-1) with the boundary and initial conditions given in Chapter 6. We applied a maximum principle, as described in [44], and were able to characterise the optimal control. This analytical work is presented in Appendix A. Further work would be to extend this analytical work to find numerical solutions and compare the results to those found both in this Chapter and in Chapter 7.

8.5 Conclusions

This Chapter has introduced optimal control for age-dependent models. We used a force of infection that implies highly associative mixing by age. By calculating the adjoint

equations and characterising the optimal control we were able to generate numerical solutions. Figure 8-2 suggests that the optimal course of vaccination is to vaccinate at high levels at a young age, with vaccination tailing off for older age groups. This supports current policy, which is to vaccinate a high proportion of females at a young age, and to offer catch-up vaccination to girls up to the age of 18 [2].

Figure 8-3 shows that the control on the sexually active females, $u_{sf}(a)$, is significantly affected when $u_{jf}(a) = 0$, with an increase in vaccination from $a \approx 15$. This may be explained by the average number of sexual partners, which peaks (in our model) at $a = 16$. This, combined with a reduced rate of individuals becoming sexually active for $a \geq 19$, may lead to increased vaccination for the age range $15 < a < 20$.

Establishing that the function $u_{sf}(a)$ is affected by the presence (or absence) of $u_{jf}(a)$, we considered $u_{sf}(a)$ for different values of c, the weighting attached to $u_{jf}(a)$ in the objective functional. Figure 8-4 shows that, for $c \geq d$ the peak in $u_{sf}(a)$ begins to occur. We found, in plotting $u_{jf}(a)$ for the same (varying) values of c, that vaccination levels for the non-sexually active become very low for $c \geq d$, making $u_{sf}(a)$ the dominant control.

Figure 8-5 shows the contrast between the cases of optimal control and constant control. Although both drive infection to very low levels, the proportion protected is much greater for the constant control case, and therefore much more costly than when following the vaccination strategy suggested by the optimal control model.

Introducing male vaccination shows that vaccination is cost effective for both males and females, and that vaccination of non-sexually active males should be at a slightly higher rate than for non-sexually active females, although this is reversed for vaccination of sexually active individuals (Figure 8-6). Removing vaccination of non-sexually active individuals shows $u_{sf}(a)$ and $u_{sm}(a)$ taking a similar form to $u_{sf}(a)$ for female-only vaccination. Figure 8-7 shows a clear difference between $u_{sf}(a)$ and $u_{sm}(a)$, with a higher proportion of females vaccinated, although it is still cost effective to vaccinate both males and females.

The analytical work for the optimal control on the PDE provides all the necessary background for finding numerical solutions. The characterisation of the optimal control shows it to be equivalent to the optimal control functions in the ODE cases. Unfortunately, the numerical solutions are very complex to program and so this falls outside the scope of this thesis. Further work would be to develop a program to find the numerical solutions and thus compare the results to those found with both the time-dependent and age-dependent ODE optimal control problems.

The results from this Chapter support current vaccination policy as being cost-effective. We show that male vaccination is also cost-effective when implemented in

the same age groups as for female vaccination. Our results also indicate that, when vaccinating sexually active individuals, it is most cost-effective to vaccinate high proportions initially, but also to have a second vaccination drive for older teenagers (between 15 and 20 years old) to maximise the success of this vaccine. Combining the results of this Chapter with those of Chapter 7 suggests that we can not only define vaccination levels over time, but also determine which age groups to target to ensure the most cost-effective strategy is employed.

Chapter 9

Conclusions

The aim of this thesis is to introduce a model that assesses the impact of vaccinating a largely non-sexually active group of individuals against a sexually transmitted infection. We consider several questions:- What is the effect of waning immunity? How do behavioural parameters affect the success of the vaccine? Is it beneficial to vaccinate males? Does introducing age-structure make a difference to the results? What is the most cost-effective way to introduce vaccination?

In Chapter 2 we construct a simple model that includes waning immunity for a vaccine that is introduced into a population. We calculate critical parameter values and the model steady states and compare the full model to its linearised counterpart. We identify certain key parameters in the model - these are the proportion of females vaccinated per unit time, p, and the parameters within R_0 - the average number of sexual partners and the average length of infection in particular.

Chapter 3 deals with the estimation of parameter values that are used in subsequent chapters. They are all calculated using data from a range of sources [3, 17, 28, 58, 61, 60] to make our model predictions as realistic as possible.

Chapter 4 presents a gender-free model that includes both waning immunity and a non-sexually active class. We find the model steady states and the "effective" R_0 value, R_0^e. In so doing, we are able to consider the effect of vaccinating individuals prior to their becoming sexually active and thus assess how the interaction between the behavioural parameter η (the rate at which individuals become sexually active) and the vaccination parameter α (the average duration of protection given by the vaccine) impacts on the potential success of the vaccine. We find that the duration of immunity has a greater impact on whether the disease could succeed in the population than the average rate at which individuals became sexually active, but a reduction in both values would have the greatest effect.

Chapter 5 develops the work of Chapter 4 by including genders in the model. We carry out similar analysis to that presented in Chapter 4 and identify the steady states and R_0^e value. The R_0^e value is equivalent to the one given in Chapter 4 - the difference between the two lies in the difference between the R_0 values in each case. As previously, we find certain critical parameter values and show that, of α and η_F, it is α that has the greater influence on the success of the vaccine - on varying α, it is possible for the disease to be eradicated, which is not the case for η_F. We also consider male vaccination, which helps to reduce infection prevalence, as expected. However, we find that we can only reduce the proportion vaccinated by $\approx 45\%$ - meaning that overall, a greater number of individuals need to be vaccinated (for our parameter set). We consider whether the introduction of a (temporarily) naturally immune class affects our results and find that there is no qualitative difference between this case and our SIS model.

In Chapter 6 we extend the model presented in Chapter 5 to an age- and time-dependent PDE model. We first consider the temporally stable state, giving an age-dependent ODE model, and solve some of the equations. We find numerical solutions for the ODE model with both constant and age-dependent parameters and two different forms of the force of infection. We find that the class profiles change significantly depending on the parameter functions and force of infection, although in all cases infection persists in the model when vaccination is included.

The second part of Chapter 6 is related to the analysis of the PDE model. We calculate the characteristics of the model and solve the system numerically. The numerical solutions show that vaccination could virtually eradicate infection within 40 years of introduction - a result that is very similar to that found with the age-dependent ODE. It differs from the results found with the time-dependent ODE (with standard parameter values), which suggest that infection would remain in the model at detectable levels even with the introduction of vaccination. We vary the $\alpha(a)$ function and find that it causes some variation in the female infection profile after 25 years, although after 50 years the differences are more pronounced. Varying the proportion of individuals vaccinated also has a large impact, with greater values of p significantly reducing the proportion of infected females after 25 years.

We consider an optimal control problem with two controls - vaccination of sexually active individuals and vaccination of non-sexually active individuals - in Chapters 7 and 8. In Chapter 7 we present a time-dependent model and Chapter 8 contains an age-dependent model. We use optimal control to assess the cost-effectiveness of the vaccine, as previous Chapters demonstrated that, whilst the vaccine may not be successful at completely eradicating the infection, it can significantly reduce the prevalence of disease

in both males and females. In Chapter 7 we find that vaccination is cost-effective for both sexually active and non-sexually active individuals. We find that the removal of, or increasing the cost weighting of, the control on sexually active individuals affects the form of the control on the non-sexually active individuals. Comparing the optimal control model to a constant control model shows that, whilst both lead to eradication of infection, a much greater level of protection (and therefore a greater cost) is used in the constant control model. Male vaccination is found to be cost effective, even when there is no cost associated with male infection, and the inclusion of temporary natural immunity does not alter the form of the control functions (which is in agreement with the findings of [50]).

Chapter 8 considers the age-dependent version of the model presented in Chapter 7. We carry out many of the same tests, and numerical solutions show that the most cost-effective method for vaccinating individuals is to vaccinate a high proportion of 12 year olds, reducing the proportion vaccinated over approximately a 10 year age span. These results support current government policy for vaccination [2]. Removing one of the controls in this model, as in Chapter 7, shows that it is the control on sexually active individuals that is most affected. In this case the control initially decreases, before increasing to a peak between the ages of 15 and 20. This is probably due to the age-dependent parameter functions, which maximise the average number of partners and the rate at which individuals become sexually active at $a \approx 16$.

We compare the optimal control problem to a constant control problem and find, as in Chapter 7, that although both types of control are successful in subduing the disease, the optimal control uses lower levels of vaccination and therefore is the cheaper solution. Male vaccination is introduced and, as in the time-dependent situation, is found to be cost-effective. On removing the controls on the non-sexually active classes the form of the remaining controls is as in the female-only vaccination case.

We discuss extending this work to applying optimal control to a PDE model. We include the characterisation of this optimal control in Appendix A. The optimal control functions in this case are equivalent to those found in both the time-dependent and age-dependent optimal control models. Further work to find numerical solutions to the PDE optimal control problem will mean that comparisons can be drawn between it and the ODE models presented in Chapters 7 and 8.

The work presented in this thesis aims to answer several questions, as posed in the introduction. We wish to assess the effect of waning immunity on the overall success, or otherwise, of the vaccine. The length of protection offered by the HPV vaccine is, as yet, unknown [18], so we vary the value of α (the average duration of protection) in our models to assess its affects. In the time-dependent gender model, we find that it is

only possible to eradicate the infection for a vaccine lasting 25 years or more. In the PDE age- and time-dependent model, a 10 year vaccine is sufficient to almost eradicate the disease after 40 years. Varying the duration of protection in the PDE model only has a small effect on the female infected class profile after 25 years. After 50 years, the impact of varying α is much greater, supporting the results from the time-dependent ODE that duration of protection from the vaccine could have a key effect on the success of the vaccine.

We consider the effect of behavioural parameters - i.e. the rate at which individuals become sexually active (η_i) and the average number of sexual partners (z_i). We find in the time-dependent gender case that varying η_i cannot force the model to the disease-free steady state for our standard parameter set. The average number of sexual partners has a much greater effect on the model and the steady state that it approaches. As z_i forms part of R_0, this is expected - z_i will affect the spread of the disease both with and without vaccination present in the model.

The next question addressed is the effect of male vaccination. We consider this both in Chapter 5 and as part of the optimal control problems in Chapters 7 and 8. We find from Chapter 5 that the introduction of male vaccination has a positive effect, but leads to a greater number of individuals needing to be vaccinated overall. However, the results from Chapters 7 and 8 show that it is cost-effective to include males in a vaccination strategy. This result is contrary to many results given in the literature, although some previous cost-effectiveness models suggested including male vaccination [39, 40].

We are also interested in how the model structure affects the results. We consider the situation using both age-dependent and time-dependent ODEs, and an age- and time- dependent PDE. We find that in both ODE scenarios, the infection cannot be eradicated with vaccination using our standard parameter set. This is at variance with the results from our PDE, which suggest that vaccination could virtually eradicate the infection after 40 years. In considering the influence of the vaccination parameters, we find that the proportion of individuals protected affects the female infected profile after 25 years, although for $p \geq 0.6$ the differences are slight. The duration of protection similarly impacts on the infection profile, especially after 50 years. This is in agreement with the time-dependent ODE, where α makes a large difference to the disease spread within the population.

Finally, we investigate the most cost-effective method for introducing the vaccine. We consider this in both the time-dependent and age-dependent case and find that the most cost-effective method over time is to start with a high proportion of individuals vaccinated and decrease the proportion over time. When considering age of vaccination,

the most cost-effective method is to vaccinate individuals at the highest rate at age 12, then decrease vaccination for older individuals. However, if vaccination is only to be applied to sexually active individuals, optimal control suggests that the highest rates of vaccination should take place both at age 12, but with a second (lower) peak at $a \approx 17$. In both cases vaccination of both sexes is indicated to be cost effective, which goes against much cost-effectiveness analysis that has recently been done on this vaccine [38, 39].

This thesis has answered many questions, but much of the work done here can be extended. More complicated functions could be formulated for some of the age-dependent parameters; this would increase complexity in the modelling, but could increase the accuracy of the quantitative results.

There are other factors that could be included in the model to investigate this problem more thoroughly. We could introduce further compartments for the different strains of the virus that are protected against by the vaccine. We could also include parameters that allow for varying 'take' or efficacy of the vaccine. Developing the model further to account for the progression to the SIL and cancer stages could indicate the role of the vaccine in potentially decreasing cervical cancer cases. When considering this, the inclusion of screening for women in the model would also be advisable. In the age-dependent case presented in Chapter 6 we do not have gender-dependent values for the number of partners an individual has, although it would be possible to include it. If this value were to be gender- as well as age-dependent it would be important to ensure that the number of partners balanced across the genders for the model to make sense.

A key extension would be to continue the optimal control problem on the PDE. Calculating numerical solutions for the PDE optimal control problem would allow comparison of the results from this and the ODE models presented in the thesis.

Another extension to the optimal control work would be an investigation into the form of the objective functional. The form used in Chapters 7 and 8 is very common [44, 52, 51], and it would be interesting to see how results generated using other forms of the objective functional compare.

In constructing mathematical models to consider the impact of vaccination against a sexually transmitted disease in a population, we find that, under our assumptions, vaccination is always recommended. The level of success of the vaccine depends on many different parameters, key amongst them the sexual behaviour of individuals and the proportion of individuals vaccinated. We find that the model structure affects the results, although none of our ODE models show eradication of infection with the standard parameter set. The most cost-effective method for implementing the vaccine is

explored and shown to support current government policy [2], although we suggest that the inclusion of males in the vaccination strategy could also be cost effective. To achieve the best results from the vaccine, we suggest that a combination of vaccination and education on sexual behaviour be undertaken, so that it may be possible to eradicate the disease from the population.

Chapter 10

Appendix A - Optimal Control applied to a PDE model

10.1 Optimal Control on the PDE

We apply the technique used in [44] to determine the characterisation of the optimal control. The PDE model is

$$\frac{\partial P_F(a,t)}{\partial t} + \frac{\partial P_F(a,t)}{\partial a} = -(\alpha(a) + \mu_F(a))P_F(a,t) + u_j(a,t)J_F(a,t) + u_s(a,t)S_F(a,t), \tag{10.1a}$$

$$\frac{\partial J_F(a,t)}{\partial t} + \frac{\partial J_F(a,t)}{\partial a} = q(\alpha)\alpha(a)P_F(a,t) - (\eta_F(a) + \mu_F(a) + u_j(a,t))J_F(a,t), \tag{10.1b}$$

$$\begin{aligned}\frac{\partial S_F(a,t)}{\partial t} + \frac{\partial S_F(a,t)}{\partial a} =& (1-q(\alpha))\alpha(a)P_F(a,t) + \eta_F(a)J_F(a,t) \\ &+ \gamma_F I_F(a,t) - (\lambda_F(a,t) + \mu_F(a) + u_s(a,t))S_F(a,t),\end{aligned} \tag{10.1c}$$

$$\frac{\partial I_F(a,t)}{\partial t} + \frac{\partial I_F(a,t)}{\partial a} = \lambda_F(a,t)S_F(a,t) - (\gamma_F + \mu_F(a))I_F(a,t), \tag{10.1d}$$

$$\frac{\partial N_F(a,t)}{\partial t} + \frac{\partial N_F(a,t)}{\partial a} = -\mu_F(a)N_F(a,t), \tag{10.1e}$$

$$\frac{\partial J_M(a,t)}{\partial t} + \frac{\partial J_M(a,t)}{\partial a} = -(\eta_M(a) + \mu_M(a))J_M(a,t), \tag{10.1f}$$

$$\frac{\partial S_M(a,t)}{\partial t} + \frac{\partial S_M(a,t)}{\partial a} = \eta_M(a)J_M(a,t) + \gamma_M I_M(a,t) - (\lambda_M(a,t) + \mu_M(a))S_M(a,t), \tag{10.1g}$$

$$\frac{\partial I_M(a,t)}{\partial t} + \frac{\partial I_M(a,t)}{\partial a} = \lambda_M(a,t)S_M(a,t) - (\gamma_M + \mu_M(a))I_M(a,t), \tag{10.1h}$$

$$\frac{\partial N_M(a,t)}{\partial t} + \frac{\partial N_M(a,t)}{\partial a} = -\mu_M(a)N_M(a,t), \tag{10.1i}$$

with boundary and initial conditions as given for the PDE model in Chapter 6 and

$$\lambda_i(a,t) = z_i(a) \int_{a_0}^{a_{max}} \frac{\beta(a,s) I_k(s,t)}{N_k(s,t) - J_k(s,t)} \quad \mathrm{d}s. \tag{10.2}$$

The objective functional is

$$\min_{\mathrm{u}} \quad J(u) = \int_{a_0}^{a_{max}} \int_0^T [A I_F(a,t) + c u_{jf}^2(a,t) + d u_{sf}^2(a,t)] \quad \mathrm{d}t\mathrm{d}a. \tag{10.3}$$

10.1.1 Sensitivity Equations

Our first step is to find the sensitivity equations (sensitivities ψ_1-ψ_7). For our model, these are as follows (we do not need to find sensitivity or adjoint equations for (10.1e) and (10.1i) as the N_i are simply the sum of the other classes):

$$
\begin{aligned}
&\frac{\partial\psi_1(a,t)}{\partial t}+\frac{\partial\psi_1(a,t)}{\partial a}+(\alpha(a)+\mu_F(a))\psi_1(a,t)-u_j(a,t)\psi_2(a,t)-u_s(a,t)\psi_3(a,t)\\
&\qquad\qquad =l_jJ_F+l_sS_F, \qquad (10.4)\\
&\frac{\partial\psi_2(a,t)}{\partial t}+\frac{\partial\psi_2(a,t)}{\partial a}-q(\alpha)\alpha(a)\psi_1(a,t)+(\eta_F(a)+\mu_F(a)+u_j(a,t))\psi_2(a,t)=-l_jJ_F,\\
&\frac{\partial\psi_3(a,t)}{\partial t}+\frac{\partial\psi_3(a,t)}{\partial a}-(1-q(\alpha))\alpha(a)\psi_1(a,t)-\eta_F(a)\psi_2(a,t)-\gamma_F\psi_4(a,t)\\
&\qquad+(\mu_F(a)+u_s(a,t))\psi_3(a,t)\\
&\qquad+z_F(a)\psi_3(a,t)\int_{a_0}^{a_{max}}\beta(a,s)\frac{I_M(s,t)}{S_M(s,t)+I_M(s,t)}\ \mathrm{d}s\\
&\qquad+z_F(a)S_F(a,t)\int_{a_0}^{a_{max}}\beta(a,s)\frac{\psi_7(s,t)S_M(s,t)-\psi_6(s,t)I_M(s,t)}{(S_M(s,t)+I_M(s,t))^2}\ \mathrm{d}s=-l_sS_F,\\
&\frac{\partial\psi_4(a,t)}{\partial t}+\frac{\partial\psi_4(a,t)}{\partial a}-z_F(a)\psi_3(a,t)\int_{a_0}^{a_{max}}\beta(a,s)\frac{I_M(s,t)}{S_M(s,t)+I_M(s,t)}\ \mathrm{d}s \qquad (10.5)\\
&\qquad-z_F(a)S_F(a,t)\int_{a_0}^{a_{max}}\beta(a,s)\frac{\psi_7(s,t)S_M(s,t)-\psi_6(s,t)I_M(s,t)}{(S_M(s,t)+I_M(s,t))^2}\ \mathrm{d}s\\
&\qquad+(\gamma_F+\mu_F(a))\psi_4(a,t)=0,\\
&\frac{\partial\psi_5(a,t)}{\partial t}+\frac{\partial\psi_5(a,t)}{\partial a}+(\eta_M(a)+\mu_M(a))\psi_5(a,t)=0,\\
&\frac{\partial\psi_6(a,t)}{\partial t}+\frac{\partial\psi_6(a,t)}{\partial a}+z_M(a)\psi_6(a,t)\int_{a_0}^{a_{max}}\beta(a,s)\frac{I_F(s,t)}{P_F(s,t)+S_F(s,t)+I_F(s,t)}\ \mathrm{d}s\\
&\qquad+z_M(a)S_M(a,t)\int_{a_0}^{a_{max}}\beta(a,s)\frac{\psi_4(s,t)(P_F(s,t)+S_F(s,t))}{(P_F(s,t)+S_F(s,t)+I_F(s,t))^2}\ \mathrm{d}s\\
&\qquad-z_M(a)S_M(a,t)\int_{a_0}^{a_{max}}\beta(a,s)\frac{(\psi_1(s,t)+\psi_3(s,t))I_F(s,t)}{(P_F(s,t)+S_F(s,t)+I_F(s,t))^2}\ \mathrm{d}s\\
&\qquad-\eta_M(a)\psi_5(a,t)-\gamma_M\psi_7(a,t)+\mu_M(a))\psi_6(a,t)=0,\\
&\frac{\partial\psi_7(a,t)}{\partial t}+\frac{\partial\psi_7(a,t)}{\partial a}-z_M(a)\psi_6(a,t)\int_{a_0}^{a_{max}}\beta(a,s)\frac{I_F(s,t)}{P_F(s,t)+S_F(s,t)+I_F(s,t)}\ \mathrm{d}s\\
&\qquad-z_M(a)S_M(a,t)\int_{a_0}^{a_{max}}\beta(a,s)\frac{\psi_4(s,t)(P_F(s,t)+S_F(s,t))}{(P_F(s,t)+S_F(s,t)+I_F(s,t))^2}\ \mathrm{d}s\\
&\qquad+z_M(a)S_M(a,t)\int_{a_0}^{a_{max}}\beta(a,s)\frac{(\psi_1(s,t)+\psi_3(s,t))I_F(s,t)}{(P_F(s,t)+S_F(s,t)+I_F(s,t))^2}\ \mathrm{d}s\\
&\qquad+(\gamma_M+\mu_M(a))\psi_7(a,t)=0.
\end{aligned}
$$

10.1.2 Adjoint Equations

As in the ODE case, we need to find the adjoint equations. In the PDE case, however, we need to use the sensitivity equations given in the section above to calculate the

adjoint equations. The relationship between the sensitivity equations is given below:

$$\mathscr{L}\begin{pmatrix}\psi_1\\ \psi_2\\ \psi_3\\ \psi_4\\ \psi_5\\ \psi_6\\ \psi_7\end{pmatrix} = \begin{pmatrix} l_j J_F + l_s S_F\\ -l_j J_F\\ -l_s S_F\\ 0\\ 0\\ 0\\ 0\end{pmatrix} \tag{10.6}$$

where

$$\mathscr{L}\begin{pmatrix}\psi_1\\ \psi_2\\ \psi_3\\ \psi_4\\ \psi_5\\ \psi_6\\ \psi_7\end{pmatrix} = \left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right)\begin{pmatrix}\psi_1\\ \psi_2\\ \psi_3\\ \psi_4\\ \psi_5\\ \psi_6\\ \psi_7\end{pmatrix} + M\begin{pmatrix}\psi_1\\ \psi_2\\ \psi_3\\ \psi_4\\ \psi_5\\ \psi_6\\ \psi_7\end{pmatrix} + \mathscr{G}\begin{pmatrix}\psi_1\\ \psi_2\\ \psi_3\\ \psi_4\\ \psi_5\\ \psi_6\\ \psi_7\end{pmatrix} \tag{10.7}$$

M is a matrix,

$$M = \begin{pmatrix} (\alpha+\mu_F) & -u_j & -u_s & 0 & \cdots\\ -q\alpha & (\eta_F+\mu_F+u_j) & 0 & 0 & \\ -(1-q)\alpha & -\eta_F & 0 & 0 & \\ 0 & 0 & \left(\mu_F(a)+u_s(a,t)+z_F(a)\int_{a_0}^{a_{max}}\beta(a,s)\frac{I_M(s,t)}{S_M(s,t)+I_M(s,t)}\ \mathrm{d}s\right) & -\gamma_F & \\ 0 & 0 & -z_F\int_{a_0}^{a_{max}}\beta(a,s)\frac{I_M(s,t)}{S_M(s,t)+I_M(s,t)}\ \mathrm{d}s & (\gamma_F+\mu_F) & \cdots\\ 0 & 0 & 0 & 0 & \\ 0 & 0 & 0 & 0 & \\ 0 & 0 & 0 & 0 & \end{pmatrix}$$

$$
\begin{pmatrix}
0 & 0 & 0 \\
0 & 0 & 0 \\
0 & 0 & 0 \\
\cdots \quad 0 & 0 & 0 \\
(\eta_M + \mu_M) & 0 & 0 \\
-\eta_M & (z_M \int_{a_0}^{a_{max}} \beta(a,s) \frac{I_F(s,t)}{P_F(s,t)+S_F(s,t)+I_F(s,t)} \, \mathrm{d}s + \mu_M) & -\gamma_M \\
0 & -z_M \int_{a_0}^{a_{max}} \beta(a,s) \frac{I_F(s,t)}{P_F(s,t)+S_F(s,t)+I_F(s,t)} \, \mathrm{d}s & (\gamma_M + \mu_M)
\end{pmatrix}
\tag{10.8}
$$

The final term is

$$
\mathscr{G} \begin{pmatrix} \psi_1 \\ \psi_2 \\ \psi_3 \\ \psi_4 \\ \psi_5 \\ \psi_6 \\ \psi_7 \end{pmatrix}
$$

$$
= \begin{pmatrix}
0 \\
0 \\
z_F(a) S_F(a,t) \int_{a_0}^{a_{max}} \beta(a,s) \frac{\psi_7(s,t) S_M(s,t) - \psi_6(s,t) I_M(s,t)}{(S_M(s,t)+I_M(s,t))^2} \, \mathrm{d}s \\
-z_F(a) S_F(a,t) \int_{a_0}^{a_{max}} \beta(a,s) \frac{\psi_7(s,t) S_M(s,t) - \psi_6(s,t) I_M(s,t)}{(S_M(s,t)+I_M(s,t))^2} \, \mathrm{d}s \\
0 \\
z_M(a) S_M(a,t) \int_{a_0}^{a_{max}} \beta(a,s) \frac{\psi_4(s,t)(P_F(s,t)+S_F(s,t)) - (\psi_1(s,t)+\psi_3(s,t)) I_F(s,t)}{(P_F(s,t)+S_F(s,t)+I_F(s,t))^2} \, \mathrm{d}s \\
-z_M(a) S_M(a,t) \int_{a_0}^{a_{max}} \beta(a,s) \frac{\psi_4(s,t)(P_F(s,t)+S_F(s,t)) - (\psi_1(s,t)+\psi_3(s,t)) I_F(s,t)}{(P_F(s,t)+S_F(s,t)+I_F(s,t))^2} \, \mathrm{d}s
\end{pmatrix}
\tag{10.9}
$$

Now we have expressed the sensitivity equations in this way, we can find the equations for the adjoints (p_1-p_7). These are related to the sensitivity equations in the following way:

$$\begin{pmatrix} p_1 & p_2 & p_3 & p_4 & p_5 & p_6 & p_7 \end{pmatrix} \cdot \mathscr{L} \begin{pmatrix} \psi_1 \\ \psi_2 \\ \psi_3 \\ \psi_4 \\ \psi_5 \\ \psi_6 \\ \psi_7 \end{pmatrix}$$

$$= \begin{pmatrix} \psi_1 & \psi_2 & \psi_3 & \psi_4 & \psi_5 & \psi_6 & \psi_7 \end{pmatrix} \cdot \mathscr{L}^* \begin{pmatrix} p_1 \\ p_2 \\ p_3 \\ p_4 \\ p_5 \\ p_6 \\ p_7 \end{pmatrix} \tag{10.10}$$

where

$$\mathscr{L}^* \begin{pmatrix} p_1 \\ p_2 \\ p_3 \\ p_4 \\ p_5 \\ p_6 \\ p_7 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ A \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{10.11}$$

with

$$\mathscr{L}^* \begin{pmatrix} p_1 \\ p_2 \\ p_3 \\ p_4 \\ p_5 \\ p_6 \\ p_7 \end{pmatrix} = -\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) \begin{pmatrix} p_1 \\ p_2 \\ p_3 \\ p_4 \\ p_5 \\ p_6 \\ p_7 \end{pmatrix} + M^{Transpose} \begin{pmatrix} p_1 \\ p_2 \\ p_3 \\ p_4 \\ p_5 \\ p_6 \\ p_7 \end{pmatrix} + \mathscr{G}^* \begin{pmatrix} p_1 \\ p_2 \\ p_3 \\ p_4 \\ p_5 \\ p_6 \\ p_7 \end{pmatrix} \tag{10.12}$$

(A comes from the objective functional and is the weighting on I_F).

To calculate $\mathscr{G}^*$, we need to return to the operators on ψ_i. In the first instance (the

nonlinear term containing ψ_6 and ψ_7 from the third sensitivity equation), we can look at

$$\begin{aligned}
&\int\int p_3(a,t)\left[z_F(a)S_F(a,t)\int \beta(a,s)\frac{\psi_7(s,t)S_M(s,t)}{(S_M(s,t)+I_M(s,t))^2}\ \mathrm{d}s\right]\mathrm{d}a\mathrm{d}t\\
&\quad-\int\int p_3(a,t)\left[z_F(a)S_F(a,t)\int \beta(a,s)\frac{\psi_6(s,t)I_M(s,t)}{(S_M(s,t)+I_M(s,t))^2}\ \mathrm{d}s\right]\mathrm{d}a\mathrm{d}t=\\
&\int\int \psi_7(s,t)\left[\frac{S_M(s,t)}{(S_M(s,t)+I_M(s,t))^2}\int z_F(a)S_F(a,t)\beta(a,s)p_3(a,t)\ \mathrm{d}a\right]\mathrm{d}s\mathrm{d}t\\
&\quad-\int\int \psi_6(s,t)\left[\frac{I_M(s,t)}{(S_M(s,t)+I_M(s,t))^2}\int z_F(a)S_F(a,t)\beta(a,s)p_3(a,t)\ \mathrm{d}a\right]\mathrm{d}s\mathrm{d}t
\end{aligned}\tag{10.13}$$

Similarly (the term from the sixth sensitivity equation containing ψ_1, ψ_3 and ψ_4),

$$\begin{aligned}
&\int\int p_6(a,t)\left[z_M(a)S_M(a,t)\int_{a_0}^{a_{max}}\beta(a,s)\frac{\psi_4(s,t)(P_F(s,t)+S_F(s,t))}{(P_F(s,t)+S_F(s,t)+I_F(s,t))^2}\ \mathrm{d}s\right]\mathrm{d}a\mathrm{d}t\\
&-\int\int p_6(a,t)\left[z_M(a)S_M(a,t)\int_{a_0}^{a_{max}}\beta(a,s)\frac{\psi_1(s,t)I_F(s,t)}{(P_F(s,t)+S_F(s,t)+I_F(s,t))^2}\ \mathrm{d}s\right]\mathrm{d}a\mathrm{d}t\\
&-\int\int p_6(a,t)\left[z_M(a)S_M(a,t)\int_{a_0}^{a_{max}}\beta(a,s)\frac{\psi_3(s,t)I_F(s,t)}{(P_F(s,t)+S_F(s,t)+I_F(s,t))^2}\ \mathrm{d}s\right]\mathrm{d}a\mathrm{d}t=\\
&\int\int \psi_4(s,t)\left[\frac{P_F(s,t)+S_F(s,t)}{(P_F(s,t)+S_F(s,t)+I_F(s,t))^2}\int_{a_0}^{a_{max}}\beta(a,s)z_M(a)S_M(a,t)p_6(a,t)\ \mathrm{d}a\right]\mathrm{d}s\mathrm{d}t\\
&-\int\int \psi_1(s,t)\left[\frac{I_F(s,t)}{(P_F(s,t)+S_F(s,t)+I_F(s,t))^2}\int_{a_0}^{a_{max}}\beta(a,s)z_M(a)S_M(a,t)p_6(a,t)\ \mathrm{d}a\right]\mathrm{d}s\mathrm{d}t\\
&-\int\int \psi_3(s,t)\left[\frac{I_F(s,t)}{(P_F(s,t)+S_F(s,t)+I_F(s,t))^2}\int_{a_0}^{a_{max}}\beta(a,s)z_M(a)S_M(a,t)p_6(a,t)\ \mathrm{d}a\right]\mathrm{d}s\mathrm{d}t
\end{aligned}\tag{10.14}$$

Note that in the equations taken from the fourth and seventh sensitivity equations, $p_3(a,t)$ will be replaced by $p_4(a,t)$ and $p_6(a,t)$ will be replaced by $p_7(a,t)$ in the above equations.

Explicitly, this gives the adjoint equations as

$$-\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)p_1(a,t)+(\alpha(a)+\mu_F(a))p_1(a,t)-q(\alpha)\alpha(a)p_2(a,t)-(1-q(\alpha))\alpha(a)p_3(a,t)$$
$$+\left(\frac{I_F(a,t)}{(P_F(a,t)+S_F(a,t)+I_F(a,t))^2}\int_{a_0}^{a_{max}}\beta(s,a)z_M(s)S_M(s,t)p_7(s,t)\quad \mathrm{d}s\right)$$
$$-\left(\frac{I_F(a,t)}{(P_F(a,t)+S_F(a,t)+I_F(a,t))^2}\int_{a_0}^{a_{max}}\beta(s,a)z_M(s)S_M(s,t)p_6(s,t)\quad \mathrm{d}s\right)=0, \tag{10.15}$$

$$-\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)p_2(a,t)-u_j(a,t)p_1(a,t)$$
$$+(\eta_F(a)+\mu_F(a)+u_j(a,t))p_2(a,t)+\eta_F(a)p_3(a,t)=0, \tag{10.16}$$

$$-\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)p_3(a,t)-u_s(a,t)p_1(a,t)$$
$$+\left(\mu_F(a)+u_s(a,t)+z_F(a)\int_{a_0}^{a_{max}}\beta(a,s)\frac{I_M(s,t)}{S_M(s,t)+I_M(s,t)}\quad \mathrm{d}s\right)p_3(a,t)$$
$$-z_F\left(\int_{a_0}^{a_{max}}\beta(a,s)\frac{I_M(s,t)}{S_M(s,t)+I_M(s,t)}\quad \mathrm{d}s\right)p_4(a,t)$$
$$+\left(\frac{I_F(a,t)}{(P_F(a,t)+S_F(a,t)+I_F(a,t))^2}\int_{a_0}^{a_{max}}\beta(s,a)z_M(s)S_M(s,t)p_7(s,t)\quad \mathrm{d}s\right)$$
$$-\left(\frac{I_F(a,t)}{(P_F(a,t)+S_F(a,t)+I_F(a,t))^2}\int_{a_0}^{a_{max}}\beta(s,a)z_M(s)S_M(s,t)p_6(s,t)\quad \mathrm{d}s\right)=0, \tag{10.17}$$

$$-\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)p_4(a,t)-\gamma_F p_3(a,t)+(\gamma_F+\mu_F(a))p_4(a,t)/$$

$$+\left(\frac{P_F(a,t)+S_F(a,t)}{(P_F(a,t)+S_F(a,t)+I_F(a,t))^2}\int_{a_0}^{a_{max}}\beta(s,a)z_M(s)S_M(s,t)p_6(s,t)\quad \mathrm{d}s\right)$$
$$-\left(\frac{P_F(a,t)+S_F(a,t)}{(P_F(a,t)+S_F(a,t)+I_F(a,t))^2}\int_{a_0}^{a_{max}}\beta(s,a)z_M(s)S_M(s,t)p_7(s,t)\quad \mathrm{d}s\right)=A, \tag{10.18}$$

$$-\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)p_5(a,t)+(\eta_M(a)+\mu_M(a))p_5(a,t)-\eta_M(a)p_6(a,t)=0, \tag{10.19}$$

$$\begin{aligned}-\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)p_6(a,t)+&\left(z_M\int_{a_0}^{a_{max}}\beta(a,s)\frac{I_F(s,t)}{P_F(s,t)+S_F(s,t)+I_F(s,t)}\ \mathrm{d}s+\mu_M\right)p_6(a,t)\\&+\left(z_M\int_{a_0}^{a_{max}}\beta(a,s)\frac{I_F(s,t)}{P_F(s,t)+S_F(s,t)+I_F(s,t)}\ \mathrm{d}s\right)p_7(a,t)\\&+\left(\frac{I_M(a,t)}{(S_M(a,t)+I_M(a,t))^2}\int z_F(s)S_F(s,t)\beta(s,a)p_4(s,t)\ \mathrm{d}s\right)\\&-\left(\frac{I_M(a,t)}{(S_M(a,t)+I_M(a,t))^2}\int z_F(s)S_F(s,t)\beta(s,a)p_3(s,t)\ \mathrm{d}s\right)=0,\end{aligned} \tag{10.20}$$

$$\begin{aligned}-\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)&p_7(a,t)-\gamma_M p_6(a,t)+(\gamma_M+\mu_M(a))p_7(a,t)\\&+\left(\frac{S_M(a,t)}{(S_M(a,t)+I_M(a,t))^2}\int z_F(s)S_F(s,t)\beta(s,a)p_3(s,t)\ \mathrm{d}s\right)\\&-\left(\frac{S_M(a,t)}{(S_M(a,t)+I_M(a,t))^2}\int z_F(s)S_F(s,t)\beta(s,a)p_4(s,t)\ \mathrm{d}s\right)=0.\end{aligned} \tag{10.21}$$

10.2 Characterisation of Optimal Control

This is calculated from the objective functional and uses difference quotients.

We start by taking

$$0\leq\lim_{\epsilon\to 0^+}\frac{J(u_j^*+\epsilon l_j,u_s^*+\epsilon l_s)-J(u_j^*,u_s^*)}{\epsilon}, \tag{10.22}$$

which gives us

$$0 \leq \lim_{\epsilon \to 0^+} \int_{a_0}^{a_{max}} \int_0^T A(\frac{I_F^\epsilon - I_F}{\epsilon}) + c((u_j^* + \epsilon l_j)^2 - (u_j^*)^2) + d((u_s^* + \epsilon l_s)^2 - (u_s^*)^2) \ \mathrm{d}a\mathrm{d}t,$$

$$= \int_{a_0}^{a_{max}} \int_0^T A\psi_4 + l_j(2cu_j^*) + l_s(2du_s^*) \ \mathrm{d}a\mathrm{d}t,$$

$$= \int_{a_0}^{a_{max}} \int_0^T \begin{pmatrix} \psi_1 & \psi_2 & \psi_3 & \psi_4 & \psi_5 & \psi_6 & \psi_7 \end{pmatrix} \begin{pmatrix} 0 \\ 0 \\ 0 \\ A \\ 0 \\ 0 \\ 0 \end{pmatrix} + l_j(2cu_j^*) + l_s(2du_s^*) \ \mathrm{d}t\mathrm{d}a, \tag{10.23}$$

$$= \int_{a_0}^{a_{max}} \int_0^T \begin{pmatrix} p_1 & p_2 & p_3 & p_4 & p_5 & p_6 & p_7 \end{pmatrix} \begin{pmatrix} l_j J_F + l_s S_F \\ -l_j J_F \\ -l_s S_F \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

$$+ l_j(2cu_j^*) + l_s(2du_s^*) \ \mathrm{d}t\mathrm{d}a, \tag{10.24}$$

$$= \int_{a_0}^{a_{max}} \int_0^T l_j(2cu_j^*(a,t) + p_1(a,t)J_F(a,t)) \ \mathrm{d}t\mathrm{d}a$$

$$+ \int_{a_0}^{a_{max}} \int_0^T l_s(2du_s^*(a,t) + p_1(a,t)S_F(a,t) - p_3(a,t)S_F(a,t)) \ \mathrm{d}t\mathrm{d}a.$$

This implies that the optimal controls are

$$u_j^*(a,t) = \frac{(p_2(a,t) - p_1(a,t))J_F(a,t)}{2c} \tag{10.25}$$

$$u_s^*(a,t) = \frac{(p_3(a,t) - p_1(a,t))S_F(a,t)}{2d}. \tag{10.26}$$

To fully complete this optimal control problem, we set bounds on both controls as $0 \leq u_j^*, u_s^* \leq 2.3$.

Interestingly, these optimal control functions are very similar to the optimal control functions found for the time-dependent ODE in Chapter 7.

Chapter 11

Appendix B - Matlab Codes

11.1 Optimal Control Code

This code is adapted from code provided with [44]; the code solves the model and adjoint equations for the gender model used in Chapter 7.

```
function y = optcodegendnew4(alpha,q,p,phi,Nf,Nfo,Nm,Nmo,z,beta,jf,jm,
etaf,etam,gammaf,gammam,Pf0,Jf0,Sf0,If0,Jm0,Sm0,Im0,A,b,c,T)

% Objective functional: J(u) = \int_0^T (A I(t) + bu(t)^2 + cv(t)^2) dt

% Set up parameter values, weighting and initial conditions

[alpha,q,p,phi,Nf,Nfo,Nm,Nmo,z,beta,jf,jm,etaf,etam,gammaf,gammam]
=paramgendforoptcont;

A=0.0001; b=0.1; c=1; T=30;
Jf0=12500; Sf0=103325; Pf0=0; If0=9175;
Jm0=12500; Sm0=103325; Im0=9175;

M = 5000; %M+1 is # nodes
t=linspace(0,T,M+1);
h=T/M;
h2 = h/2;

% Set up initial matrix values for classes
```

```
Jf=zeros(1,M+1); Sf=zeros(1,M+1); Pf=zeros(1,M+1); If=zeros(1,M+1);
Jm=zeros(1,M+1); Sm=zeros(1,M+1); Im=zeros(1,M+1);

Jf(1)=Jf0; Sf(1)=Sf0; Pf(1)=Pf0; If(1)=If0;
Jm(1)=Jm0; Sm(1)=Sm0; Im(1)=Im0;

% Set up initial values for adjoints

lambda1=zeros(1,M+1); lambda2=zeros(1,M+1); lambda3=zeros(1,M+1);
lambda4=zeros(1,M+1); lambda5=zeros(1,M+1); lambda6=zeros(1,M+1);
lambda7=zeros(1,M+1);

% Set up initial value for u

u=zeros(1,M+1); v=zeros(1,M+1);

% Convergence test
test2=1;
errlim=0.000001;
while test2>errlim
    disp(['TEST = ',num2str(test2)])

    oldu = u; oldv = v;
    oldJf = Jf; oldSf = Sf; oldPf = Pf; oldIf = If;
    oldJm = Jm; oldSm = Sm; oldIm = Im;
    oldlambda1 = lambda1; oldlambda2 = lambda2; oldlambda3 = lambda3;
    oldlambda4 = lambda4; oldlambda5 = lambda5; oldlambda6 = lambda6;
    oldlambda7 = lambda7;

    % Setting up numerical solution of differential equations

    for i = 1:M
        m11 = jf*(Nf/phi)-(etaf+u(i)+1/phi)*Jf(i)+q*alpha*Pf(i);
        m12 = (1-jf)*(Nf/phi)+etaf*Jf(i)+(1-q)*alpha*Pf(i)
        -((z*beta)/(Nm-Jm(i)))*Sf(i)*Im(i)-(1/phi+v(i))*Sf(i)
        +gammaf*If(i);
        m13 = u(i)*Jf(i)+v(i)*Sf(i)-(alpha+1/phi)*Pf(i);
```

```
 m14 = ((z*beta)/(Nm-Jm(i)))*Sf(i)*Im(i)-(gammaf+1/phi)*If(i);
 m15 = jm*(Nm/phi)-(etam+1/phi)*Jm(i);
 m16 = (1-jm)*(Nm/phi)+etam*Jm(i)-((z*beta)/(Nf-Jf(i)))*Sm(i)*If(i)
 -(1/phi)*Sm(i)+gammam*Im(i);
 m17 = ((z*beta)/(Nf-Jf(i)))*Sm(i)*If(i)-(gammam+1/phi)*Im(i);

 m21 = jf*(Nf/phi)-(etaf+0.5*(u(i)+u(i+1))+1/phi)*(Jf(i)+h2*m11)
 +q*alpha*(Pf(i)+h2*m13);
 m22 = (1-jf)*(Nf/phi)+etaf*(Jf(i)+h2*m11)+(1-q)*alpha*(Pf(i)+h2*m13)
-((z*beta)/(Nm-(Jm(i)+h2*m15)))*(Sf(i)+h2*m12)*(Im(i)+h2*m17)
-(1/phi+0.5*(v(i)+v(i+1)))*(Sf(i)+h2*m12)+gammaf*(If(i)+h2*m14);
 m23 = 0.5*(u(i)+u(i+1))*(Jf(i)+h2*m11)
 +0.5*(v(i)+v(i+1))*(Sf(i)+h2*m12)-(alpha+1/phi)*(Pf(i)+h2*m13);
 m24 = ((z*beta)/(Nm-(Jm(i)+h2*m15)))*(Sf(i)+h2*m12)*(Im(i)+h2*m17)
 -(gammaf+1/phi)*(If(i)+h2*m14);
 m25 = jm*(Nm/phi)-(etam+1/phi)*(Jm(i)+h2*m15);
 m26 = (1-jm)*(Nm/phi)+etam*(Jm(i)+h2*m15)
 -((z*beta)/(Nf-(Jf(i)+h2*m11)))*(Sm(i)+h2*m16)*(If(i)+h2*m14)
 -(1/phi)*(Sm(i)+h2*m16)+gammam*(Im(i)+h2*m17);
 m27 = ((z*beta)/(Nf-(Jf(i)+h2*m11)))*(Sm(i)+h2*m16)*(If(i)+h2*m14)
 -(gammam+1/phi)*(Im(i)+h2*m17);

 m31 = jf*(Nf/phi)-(etaf+0.5*(u(i)+u(i+1))+1/phi)*(Jf(i)+h2*m21)
 +q*alpha*(Pf(i)+h2*m23);
 m32 = (1-jf)*(Nf/phi)+etaf*(Jf(i)+h2*m21)+(1-q)*alpha*(Pf(i)+h2*m23)
 -((z*beta)/(Nm-(Jm(i)+h2*m25)))*(Sf(i)+h2*m22)*(Im(i)+h2*m27)
 -(1/phi+0.5*(v(i)+v(i+1)))*(Sf(i)+h2*m22)+gammaf*(If(i)+h2*m24);
 m33 = 0.5*(u(i)+u(i+1))*(Jf(i)+h2*m21)+0.5*(v(i)+v(i+1))*(Sf(i)+h2*m22)
 -(alpha+1/phi)*(Pf(i)+h2*m23);
 m34 = ((z*beta)/(Nm-(Jm(i)+h2*m25)))*(Sf(i)+h2*m22)*(Im(i)+h2*m27)
 -(gammaf+1/phi)*(If(i)+h2*m24);
 m35 = jm*(Nm/phi)-(etam+1/phi)*(Jm(i)+h2*m25);
 m36 = (1-jm)*(Nm/phi)+etam*(Jm(i)+h2*m25)
 -((z*beta)/(Nf-(Jf(i)+h2*m21)))*(Sm(i)+h2*m26)*(If(i)+h2*m24)
 -(1/phi)*(Sm(i)+h2*m26)+gammam*(Im(i)+h2*m27);
 m37 = ((z*beta)/(Nf-(Jf(i)+h2*m21)))*(Sm(i)+h2*m26)*(If(i)+h2*m24)
 -(gammam+1/phi)*(Im(i)+h2*m27);
```

```
    m41 = jf*(Nf/phi)-(etaf+u(i+1)+1/phi)*(Jf(i)+h*m31)
    +q*alpha*(Pf(i)+h*m33);
    m42 = (1-jf)*(Nf/phi)+etaf*(Jf(i)+h*m31)+(1-q)*alpha*(Pf(i)+h*m33)
    -((z*beta)/(Nm-(Jm(i)+h*m35)))*(Sf(i)+h*m32)*(Im(i)+h*m37)
    -(1/phi+v(i+1))*(Sf(i)+h*m32)+gammaf*(If(i)+h*m34);
    m43 = u(i+1)*(Jf(i)+h*m31)+v(i+1)*(Sf(i)+h*m32)
    -(alpha+1/phi)*(Pf(i)+h*m33);
    m44 = ((z*beta)/(Nm-(Jm(i)+h*m35)))*(Sf(i)+h*m32)*(Im(i)+h*m37)
    -(gammaf+1/phi)*(If(i)+h*m34);
    m45 = jm*(Nm/phi)-(etam+1/phi)*(Jm(i)+h*m35);
    m46 = (1-jm)*(Nm/phi)+etam*(Jm(i)+h*m35)
    -((z*beta)/(Nf-(Jf(i)+h*m31)))*(Sm(i)+h*m36)*(If(i)+h*m34)
    -(1/phi)*(Sm(i)+h*m36)+gammam*(Im(i)+h*m37);
    m47 = ((z*beta)/(Nf-(Jf(i)+h*m31)))*(Sm(i)+h*m36)*(If(i)+h*m34)
    -(gammam+1/phi)*(Im(i)+h*m37);

    Jf(i+1) = Jf(i) + (h/6)*(m11 + 2*m21 + 2*m31 + m41);
    Sf(i+1) = Sf(i) + (h/6)*(m12 + 2*m22 + 2*m32 + m42);
    Pf(i+1) = Pf(i) + (h/6)*(m13 + 2*m23 + 2*m33 + m43);
    If(i+1) = If(i) + (h/6)*(m14 + 2*m24 + 2*m34 + m44);
    Jm(i+1) = Jm(i) + (h/6)*(m15 + 2*m25 + 2*m35 + m45);
    Sm(i+1) = Sm(i) + (h/6)*(m16 + 2*m26 + 2*m36 + m46);
    Im(i+1) = Im(i) + (h/6)*(m17 + 2*m27 + 2*m37 + m47);
end

% Setting up adjoint equations

for i = 1:M
    j = M + 2 - i;
    m11 = -b*u(j)*u(j)+(etaf+u(j)+1/phi)*lambda1(j)-etaf*lambda2(j)
    -u(j)*lambda3(j)
    +((z*beta*If(j)*Sm(j))/(Nf-Jf(j))^2)*lambda6(j)
    -((z*beta*If(j)*Sm(j))/(Nf-Jf(j))^2)*lambda7(j);
    m12 = -c*v(j)*v(j)-v(j)*lambda3(j)
    +(((z*beta*Im(j))/(Nm-Jm(j)))+v(j)+1/phi)*lambda2(j)
    -((z*beta*Im(j))/(Nm-Jm(j)))*lambda4(j);
```

```
m13 = -q*alpha*lambda1(j)-(1-q)*alpha*lambda2(j)
+(alpha+1/phi)*lambda3(j);
m14 = -A-gammaf*lambda2(j)+(gammaf+1/phi)*lambda4(j)
+((z*beta*Sm(j))/(Nf-Jf(j)))*lambda6(j)
-((z*beta*Sm(j))/(Nf-Jf(j)))*lambda7(j);
m15 = (etam+1/phi)*lambda5(j)-etam*lambda6(j)
+((z*beta*Sf(j)*Im(j))/((Nm-Jm(j))^2))*lambda2(j)
-((z*beta*Sf(j)*Im(j))/((Nm-Jm(j))^2))*lambda4(j);
m16 = (((z*beta*If(j))/(Nf-Jf(j)))+1/phi)*lambda6(j)
-((z*beta*If(j))/(Nf-Jf(j)))*lambda7(j);
m17 = ((z*beta*Sf(j))/(Nm-Jm(j)))*lambda2(j)
-((z*beta*Sf(j))/(Nm-Jm(j)))*lambda4(j)
-gammam*lambda6(j)+(gammam+1/phi)*lambda7(j);

m21 = -b*0.5*(u(j)+u(j-1))*0.5*(u(j)+u(j-1))
+(etaf+0.5*(u(j)+u(j-1))+1/phi)*(lambda1(j)-h2*m11)
-etaf*(lambda2(j)-h2*m12)-0.5*(u(j)+u(j-1))*(lambda3(j)-h2*m13)
+((z*beta*0.5*(If(j)+If(j-1))*0.5*(Sm(j)+Sm(j-1)))/...
...(Nf-0.5*(Jf(j)+Jf(j-1)))^2)*(lambda6(j)-h2*m16)
-((z*beta*0.5*(If(j)+If(j-1))*0.5*(Sm(j)+Sm(j-1)))/...
...(Nf-0.5*(Jf(j)+Jf(j-1)))^2)*(lambda7(j)-h2*m17);
m22 = -c*0.5*(v(j)+v(j-1))*0.5*(v(j)+v(j-1))
+(((z*beta*0.5*(Im(j)+Im(j-1)))/(Nm-0.5*(Jm(j)+Jm(j-1))))
+0.5*(v(j)+v(j-1))+1/phi)*(lambda2(j)-h2*m12)
-0.5*(v(j)+v(j-1))*(lambda3(j)-h2*m13)
-((z*beta*0.5*(Im(j)+Im(j-1)))/(Nm-0.5*(Jm(j)+Jm(j-1))))*...
...(lambda4(j)-h2*m14);
m23 = -q*alpha*(lambda1(j)-h2*m11)-(1-q)*alpha*(lambda2(j)-h2*m12)
+(alpha+1/phi)*(lambda3(j)-h2*m13);
m24 = -A-gammaf*(lambda2(j)-h2*m12)+(gammaf+1/phi)*(lambda4(j)-h2*m14)
+((z*beta*0.5*(Sm(j)+Sm(j-1)))/(Nf-0.5*(Jf(j)+Jf(j-1))))*...
...(lambda6(j)-h2*m16)
-((z*beta*0.5*(Sm(j)+Sm(j-1)))/(Nf-0.5*(Jf(j)+Jf(j-1))))*...
...(lambda7(j)-h2*m17);
m25 = (etam+1/phi)*(lambda5(j)-h2*m15)-etam*(lambda6(j)-h2*m16)
+((z*beta*0.5*(Sf(j)+Sf(j-1))*0.5*(Im(j)+Im(j-1)))/...
...((Nm-0.5*(Jm(j)+Jm(j-1)))^2))*(lambda2(j)-h2*m12)
```

```
      -((z*beta*0.5*(Sf(j)+Sf(j-1))*0.5*(Im(j)+Im(j-1)))/...
      ...((Nm-0.5*(Jm(j)+Jm(j-1)))^2))*(lambda4(j)-h2*m14);
      m26 = (((z*beta*0.5*(If(j)+If(j-1)))/...
      ...(Nf-0.5*(Jf(j)+Jf(j-1))))+1/phi)*...
...(lambda6(j)-h2*m16)-((z*beta*0.5*(If(j)+If(j-1)))/...
      ...(Nf-0.5*(Jf(j)+Jf(j-1))))*(lambda7(j)-h2*m17);
      m27 = ((z*beta*0.5*(Sf(j)+Sf(j-1)))/...
      ...(Nm-0.5*(Jm(j)+Jm(j-1))))*(lambda2(j)-h2*m12)
      -((z*beta*0.5*(Sf(j)+Sf(j-1)))/...
      ...(Nm-0.5*(Jm(j)+Jm(j-1))))*(lambda4(j)-h2*m14)
      -gammam*(lambda6(j)-h2*m16)+(gammam+1/phi)*(lambda7(j)-h2*m17);

      m31 = -b*0.5*(u(j)+u(j-1))*0.5*(u(j)+u(j-1))
      +(etaf+0.5*(u(j)+u(j-1))+1/phi)*(lambda1(j)-h2*m21)
      -etaf*(lambda2(j)-h2*m22)-0.5*(u(j)+u(j-1))*(lambda3(j)-h2*m23)
      +((z*beta*0.5*(If(j)+If(j-1))*0.5*(Sm(j)+Sm(j-1)))/...
      ...(Nf-0.5*(Jf(j)+Jf(j-1)))^2)*(lambda6(j)-h2*m26)
      -((z*beta*0.5*(If(j)+If(j-1))*0.5*(Sm(j)+Sm(j-1)))/...
      ...(Nf-0.5*(Jf(j)+Jf(j-1)))^2)*(lambda7(j)-h2*m27);
      m32 = -c*0.5*(v(j)+v(j-1))*0.5*(v(j)+v(j-1))
      +(((z*beta*0.5*(Im(j)+Im(j-1)))/(Nm-0.5*(Jm(j)+Jm(j-1))))
      +0.5*(v(j)+v(j-1))+1/phi)*(lambda2(j)-h2*m22)
      -0.5*(v(j)+v(j-1))*(lambda3(j)-h2*m23)
      -((z*beta*0.5*(Im(j)+Im(j-1)))/...
      ...(Nm-0.5*(Jm(j)+Jm(j-1))))*(lambda4(j)-h2*m24);
      m33 = -q*alpha*(lambda1(j)-h2*m21)-(1-q)*alpha*(lambda2(j)-h2*m22)
      +(alpha+1/phi)*(lambda3(j)-h2*m23);
      m34 = -A-gammaf*(lambda2(j)-h2*m22)+(gammaf+1/phi)*...
      ...(lambda4(j)-h2*m24)
      +((z*beta*0.5*(Sm(j)+Sm(j-1)))/(Nf-0.5*(Jf(j)+Jf(j-1))))*...
      ...(lambda6(j)-h2*m26)
      -((z*beta*0.5*(Sm(j)+Sm(j-1)))/(Nf-0.5*(Jf(j)+Jf(j-1))))*...
      ...(lambda7(j)-h2*m27);
      m35 = (etam+1/phi)*(lambda5(j)-h2*m25)-etam*(lambda6(j)-h2*m26)
      +((z*beta*0.5*(Sf(j)+Sf(j-1))*0.5*(Im(j)+Im(j-1)))/...
      ...((Nm-0.5*(Jm(j)+Jm(j-1)))^2))*(lambda2(j)-h2*m12)
      -((z*beta*0.5*(Sf(j)+Sf(j-1))*0.5*(Im(j)+Im(j-1)))/...
```

```
...((Nm-0.5*(Jm(j)+Jm(j-1)))^2))*(lambda4(j)-h2*m14);
m36 = (((z*beta*0.5*(If(j)+If(j-1)))/(Nf-0.5*(Jf(j)+Jf(j-1))))+...
...1/phi)*(lambda6(j)-h2*m26)
-((z*beta*0.5*(If(j)+If(j-1)))/(Nf-0.5*(Jf(j)+Jf(j-1))))*...
...(lambda7(j)-h2*m27);
m37 = ((z*beta*0.5*(Sf(j)+Sf(j-1)))/(Nm-0.5*(Jm(j)+Jm(j-1))))*...
...(lambda2(j)-h2*m22)
-((z*beta*0.5*(Sf(j)+Sf(j-1)))/(Nm-0.5*(Jm(j)+Jm(j-1))))*...
...(lambda4(j)-h2*m24)
-gammam*(lambda6(j)-h2*m26)+(gammam+1/phi)*(lambda7(j)-h2*m27);

m41 = -b*u(j-1)*u(j-1)
+(etaf+u(j-1)+1/phi)*(lambda1(j)-h*m31)-etaf*(lambda2(j)-h*m32)
-u(j-1)*(lambda3(j)-h*m33)
+((z*beta*If(j-1)*Sm(j-1))/(Nf-Jf(j-1))^2)*(lambda6(j)-h*m36)
-((z*beta*If(j-1)*Sm(j-1))/(Nf-Jf(j-1))^2)*(lambda7(j)-h*m37);
m42 = -c*v(j-1)*v(j-1)
+(((z*beta*Im(j-1))/(Nm-Jm(j-1)))+v(j-1)+1/phi)*(lambda2(j)-h*m32)
-v(j-1)*(lambda3(j)-h*m33)-((z*beta*Im(j-1))/(Nm-Jm(j-1)))*...
...(lambda4(j)-h*m34);
m43 = -q*alpha*(lambda1(j)-h*m31)-(1-q)*alpha*(lambda2(j)-h*m32)
+(alpha+1/phi)*(lambda3(j)-h*m33);
m44 = -A-gammaf*(lambda2(j)-h*m32)+(gammaf+1/phi)*(lambda4(j)-h*m34)
+((z*beta*Sm(j-1))/(Nf-Jf(j-1)))*(lambda6(j)-h*m36)
-((z*beta*Sm(j-1))/(Nf-Jf(j-1)))*(lambda7(j)-h*m37);
m45 = (etam+1/phi)*(lambda5(j)-h*m35)-etam*(lambda6(j)-h*m36)
+((z*beta*Sf(j-1)*Im(j-1))/((Nm-Jm(j-1))^2))*(lambda2(j)-h*m32)
-((z*beta*Sf(j-1)*Im(j-1))/((Nm-Jm(j-1))^2))*(lambda4(j)-h*m34);
m46 = (((z*beta*If(j-1))/(Nf-Jf(j-1)))+1/phi)*(lambda6(j)-h*m36)
-((z*beta*If(j-1))/(Nf-Jf(j-1)))*(lambda7(j)-h*m37);
m47 = ((z*beta*Sf(j-1))/(Nm-Jm(j-1)))*(lambda2(j)-h*m32)
-((z*beta*Sf(j-1))/(Nm-Jm(j-1)))*(lambda4(j)-h*m34)
-gammam*(lambda6(j)-h*m36)+(gammam+1/phi)*(lambda7(j)-h*m37);

lambda1(j-1) = lambda1(j) - (h/6)*(m11 + 2*m21 + 2*m31 + m41);
lambda2(j-1) = lambda2(j) - (h/6)*(m12 + 2*m22 + 2*m32 + m42);
lambda3(j-1) = lambda3(j) - (h/6)*(m13 + 2*m23 + 2*m33 + m43);
```

```
        lambda4(j-1) = lambda4(j) - (h/6)*(m14 + 2*m24 + 2*m34 + m44);
        lambda5(j-1) = lambda5(j) - (h/6)*(m15 + 2*m25 + 2*m35 + m45);
        lambda6(j-1) = lambda6(j) - (h/6)*(m16 + 2*m26 + 2*m36 + m46);
        lambda7(j-1) = lambda7(j) - (h/6)*(m17 + 2*m27 + 2*m37 + m47);
    end


% Characterising the optimal control functions
  tempu=(lambda1-lambda3)./(2*b);
%  tempu=0;
    u1 = min(2.3,max(0,tempu)); %temporary u
    u = 0.5*(u1 + oldu); % final control
  tempv=(lambda2-lambda3)./(2*c);
 %  tempv=0;
    v1 = min(2.3,max(0,tempv)); %temporary v
    v = 0.5*(v1 + oldv);

%Convergence test parameters

    temp1 = sum(abs(oldu - u));
    temp2 = sum(abs(oldv - v));
    temp3 = sum(abs(oldJf - Jf));
    temp4 = sum(abs(oldSf - Sf));
    temp5 = sum(abs(oldPf - Pf));
    temp6 = sum(abs(oldIf - If));
    temp7 = sum(abs(oldJm - Jm));
    temp8 = sum(abs(oldSm - Sm));
    temp9 = sum(abs(oldIm - Im));
    temp10 = sum(abs(oldlambda1 - lambda1));
    temp11 = sum(abs(oldlambda2 - lambda2));
    temp12 = sum(abs(oldlambda3 - lambda3));
    temp13 = sum(abs(oldlambda4 - lambda4));
    temp14 = sum(abs(oldlambda5 - lambda5));
    temp15 = sum(abs(oldlambda6 - lambda6));
    temp16 = sum(abs(oldlambda7 - lambda7));

test2 = max([temp1 temp2 temp3 temp4 temp5 temp6 temp7
```

```
temp8 temp9 temp10 temp11 temp12 temp13 temp14 temp15 temp16]);
end


%Final Values
y(1,:) = t;
y(2,:) = Jf;
y(3,:) = Sf;
y(4,:) = Pf;
y(5,:) = If;
y(6,:) = Jm;
y(7,:) = Sm;
y(8,:) = Im;
y(9,:) = u;
y(10,:) = v;

% Plot the optimal functions

figure(3)
set(gca,'FontSize',14)
set(legend,'FontSize',14)
plot(y(1,:),y(9,:), 'k','LineWidth',3)
hold on
plot(y(1,:),y(10,:), '--k','LineWidth',3)
hold on
xlabel('t','FontSize',14)
ylabel('Optimal control','FontSize',14)
legend('u_{jf}(t)','u_{sf}(t)')


% Plot the class profiles

figure(6)
set(gca,'FontSize',14)
set(legend,'FontSize',14)
plot(y(1,:),y(2,:),'--k','LineWidth',3)
hold on
```

```
plot(y(1,:),y(3,:),'-.k','LineWidth',3)
hold on
plot(y(1,:),y(4,:),'k','LineWidth',3)
hold on
plot(y(1,:),y(5,:),':k','LineWidth',3)
hold on
plot(y(1,:),y(6,:),'--', 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
plot(y(1,:),y(7,:),'-.', 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
plot(y(1,:),y(8,:),':', 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
xlabel('t','FontSize',14)
ylabel('Classes','FontSize',14)
legend('J_F(t)','S_F(t)','P_F(t)','I_F(t)', 'J_M(t)', 'S_M(t)', 'I_M(t)')
```

11.2 Age-dependent ODE code

```
[p,alpha,q,phi,Nf,Nfo,Nm,Nmo,z,beta,jf,jm,etaf,etam,gammaf,gammam,mu]
=paramgend;

% Setting up initial conditions

T=65;
Pf0=87500; Jf0=28125; Sf0=3125; If0=6250;
Jm0=106875; Sm0=11875; Im0=6250;
Nf0=125000; Nm0=125000;

% Set up values for some parameters

M = 1000; %M+1 is # nodes
t=linspace(0,T,M+1);
h=T/M;
h2 = h/2;

% Set up initial values for classes
```

```
Pf=zeros(1,M+1); Jf=zeros(1,M+1); Sf=zeros(1,M+1); If=zeros(1,M+1);
Jm=zeros(1,M+1); Sm=zeros(1,M+1); Im=zeros(1,M+1);
Nf=zeros(1,M+1); Nm=zeros(1,M+1);

lambdaf(1,M+1)=1; lambdam(1,M+1)=1;

test2=1;
kk=0;

errlim=0.000000001;
while test2>errlim
    kk=kk+1;
    disp(['IT = ',num2str(kk),' TEST = ',num2str(test2)])


Pf(1)=Pf0; Jf(1)=Jf0; Sf(1)=Sf0; If(1)=If0; Nf(1)=Nf0;
Jm(1)=Jm0; Sm(1)=Sm0; Im(1)=Im0; Nm(1)=Nm0;

    oldPf = Pf; oldJf = Jf; oldSf = Sf; oldIf = If; oldNf = Nf;
    oldJm = Jm; oldSm = Sm; oldIm = Im; oldNm = Nm;
    oldlambdaf=lambdaf; oldlambdam=lambdam;

% Solving the model equations

for i = 1:M
    j=(i)./(M./T);
        %disp(i)
        m11 = -(alpha+mu)*Pf(i);
        m12 = -(etaf+mu)*Jf(i)+q*alpha*Pf(i) ;
        m13 = (1-q)*alpha*Pf(i)+etaf*Jf(i)-(z*beta*Sf(i)*lambdaf(i))
        +gammaf*If(i)-mu*Sf(i);
        m14 = (z*beta*Sf(i)*lambdaf(i))-(gammaf+mu)*If(i);
        m15 = -mu*Nf(i);
        m16 = -(etam+mu)*Jm(i);
        m17 = etam*Jm(i)-(z*beta*Sm(i)*lambdam(i))+gammam*Im(i)-mu*Sm(i);
        m18 = (z*beta*Sm(i)*lambdam(i))-(gammam+mu)*Im(i);
        m19 = -mu*Nm(i);
```

```
m21 = -(alpha+mu)*(Pf(i)+h2*m11);
m22 = -(etaf+mu)*(Jf(i)+h2*m12)+q*alpha*(Pf(i)+h2*m11) ;
m23 = (1-q)*alpha*(Pf(i)+h2*m11)+etaf*(Jf(i)+h2*m12)
-(z*beta*(Sf(i)+h2*m13)*lambdaf(i))+gammaf*(If(i)+h2*m14)
-mu*(Sf(i)+h2*m13);
m24 = (z*beta*(Sf(i)+h2*m13)*lambdaf(i))-(gammaf+mu)*(If(i)+h2*m14);
m25 = -mu*(Nf(i)+h2*m15);
m26 = -(etam+mu)*(Jm(i)+h2*m16);
m27 = etam*(Jm(i)+h2*m16)-(z*beta*(Sm(i)+h2*m17)*lambdam(i))
+gammam*(Im(i)+h2*m18)-mu*(Sm(i)+h2*m17);
m28 = (z*beta*(Sm(i)+h2*m17)*lambdam(i))-(gammam+mu)*(Im(i)+h2*m18);
m29 = -mu*(Nm(i)+h2*m19);

m31 = -(alpha+mu)*(Pf(i)+h2*m21);
m32 = -(etaf+mu)*(Jf(i)+h2*m22)+q*alpha*(Pf(i)+h2*m21) ;
m33 = (1-q)*alpha*(Pf(i)+h2*m21)+etaf*(Jf(i)+h2*m22)
-(z*beta*(Sf(i)+h2*m23)*lambdaf(i))+gammaf*(If(i)+h2*m24)
-mu*(Sf(i)+h2*m23);
m34 = (z*beta*(Sf(i)+h2*m23)*lambdaf(i))-(gammaf+mu)*(If(i)+h2*m24);
m35 = -mu*(Nf(i)+h2*m25);
m36 = -(etam+mu)*(Jm(i)+h2*m26);
m37 = etam*(Jm(i)+h2*m26)-(z*beta*(Sm(i)+h2*m27)*lambdam(i))
+gammam*(Im(i)+h2*m28)-mu*(Sm(i)+h2*m27);
m38 = (z*beta*(Sm(i)+h2*m27)*lambdam(i))-(gammam+mu)*(Im(i)+h2*m28);
m39 = -mu*(Nm(i)+h2*m29);

m41 = -(alpha+mu)*(Pf(i)+h*m31);
m42 = -(etaf+mu)*(Jf(i)+h*m32)+q*alpha*(Pf(i)+h*m31) ;
m43 = (1-q)*alpha*(Pf(i)+h*m31)+etaf*(Jf(i)+h*m32)
-(z*beta*(Sf(i)+h*m33)*lambdaf(i))+gammaf*(If(i)+h*m34)
-mu*(Sf(i)+h*m33);
m44 = (z*beta*(Sf(i)+h*m33)*lambdaf(i))-(gammaf+mu)*(If(i)+h*m34);
m45 = -mu*(Nf(i)+h*m35);
m46 = -(etam+mu)*(Jm(i)+h*m36);
m47 = etam*(Jm(i)+h*m36)-(z*beta*(Sm(i)+h*m37)*lambdam(i))
+gammam*(Im(i)+h*m38)-mu*(Sm(i)+h*m37);
```

```
        m48 = (z*beta*(Sm(i)+h*m37)*lambdam(i))-(gammam+mu)*(Im(i)+h*m38);
        m49 = -mu*(Nm(i)+h*m39);

        Pf(i+1) = Pf(i) + (h/6)*(m11 + 2*m21 + 2*m31 + m41);
        Jf(i+1) = Jf(i) + (h/6)*(m12 + 2*m22 + 2*m32 + m42);
        Sf(i+1) = Sf(i) + (h/6)*(m13 + 2*m23 + 2*m33 + m43);
        If(i+1) = If(i) + (h/6)*(m14 + 2*m24 + 2*m34 + m44);
        Nf(i+1) = Nf(i) + (h/6)*(m15 + 2*m25 + 2*m35 + m45);
        Jm(i+1) = Jm(i) + (h/6)*(m16 + 2*m26 + 2*m36 + m46);
        Sm(i+1) = Sm(i) + (h/6)*(m17 + 2*m27 + 2*m37 + m47);
        Im(i+1) = Im(i) + (h/6)*(m18 + 2*m28 + 2*m38 + m48);
        Nm(i+1) = Nm(i) + (h/6)*(m19 + 2*m29 + 2*m39 + m49);


    end

% Calculating mixing matrix

A=zeros(M+1,M+1);
  for i=1:M+1;
      for j=1:M+1;
          if j==i;
      A(i,j)=0.5;
          elseif j==i+1;
      A(i,j)=0.25-0.125;
          elseif j==i-1;
      A(i,j)=0.25-0.125;
       elseif j==i+2;
      A(i,j)=0.125;
          elseif j==i-2;
      A(i,j)=0.125;
         end


       end
  end
  A(1,2)=0.25; A(1,3)=0.25; A(2,1)=0.25;
```

```
  A(M,M+1)=0.25; A(M+1,M-1)=0.25; A(M+1,M)=0.25;


    % Calculating the integral part of the force of infection

    for i=1:M+1;
  lambdaf(i)=sum(A(i,:).*(Im)./(Nm-Jm));
  lambdam(i)=sum(A(i,:).*(If)./(Nf-Jf));

  end

    temp1 = sum(abs(oldPf - Pf)); temp2 = sum(abs(oldJf - Jf));
    temp3 = sum(abs(oldSf - Sf)); temp4 = sum(abs(oldIf - If));
    temp5 = sum(abs(oldJm - Jm)); temp6 = sum(abs(oldSm - Sm));
    temp7 = sum(abs(oldIm - Im)); temp8 = sum(abs(oldNf - Nf));
    temp9 = sum(abs(oldNm - Nm));
    temp10 = sum(abs(oldlambdaf - lambdaf));
    temp11 = sum(abs(oldlambdam - lambdam));

test2 = max([temp1 temp2 temp3 temp4 temp5 temp6 ...
... temp7 temp8 temp9 temp10 temp11]);

end

y(1,:) = t;
y(2,:) = Pf; y(3,:) = Jf; y(4,:) = Sf; y(5,:) = If; y(6,:) = Nf;
y(7,:) = Jm; y(8,:) = Sm; y(9,:) = Im; y(10,:) = Nm;
y(11,:) = lambdaf; y(12,:) = lambdam;

figure(2)
set(gca,'FontSize',14)
  set(legend,'FontSize',14)
plot((y(1,:)+12),y(2,:)/125000,'LineWidth',3)
 hold on
 plot((y(1,:)+12),y(3,:)/125000,'--k','LineWidth',3)
 hold on
plot((y(1,:)+12),y(4,:)/125000,'-.k','LineWidth',3)
```

```
 hold on
plot((y(1,:)+12),y(5,:)/125000,':k','LineWidth',3)
hold on
plot((y(1,:)+12),y(6,:)/125000,'k','LineWidth',3)
hold on
plot((y(1,:)+12),y(7,:)/125000,'--', 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
plot((y(1,:)+12),y(8,:)/125000,'-.', 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
plot((y(1,:)+12),y(9,:)/125000,':', 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
plot((y(1,:)+12),y(10,:)/125000, 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
legend('P_F', 'J_F', 'S_F', 'I_F', 'N_F', 'J_M', 'S_M', 'I_M', 'N_M')
xlabel('age')
ylabel('Population')
figure(3)
set(gca,'FontSize',14)
  set(legend,'FontSize',14)
plot((y(1,:)+12),y(5,:)/125000,'k','LineWidth',3)
hold on
plot((y(1,:)+12),y(9,:)/125000, 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
xlabel('age')
ylabel('Proportion Infected')
```

11.3 Matlab Code for PDE Model

```
%This program will use the ENO UNO scheme (Essentially Non-Oscillatory
% Uniformly high Order) to do the advection.

%Ref Harten, A. and Osher, S.
%Uniformly High-Order Accurate Nonoscillatory Schemes. I.
%SIAM Journal on Numerical Analysis, 24, 2, 279-309. 1987

clear; clc;

% Set up grid
```

```
n=148; da=1/n; a=(12:0.5:85.5); C=0.1; dt=C.*da; c=dt./da;

% Final Time

N1=n/C; % Final time is N2*dt*74
N2=800;
p=0.7;
Nf=125000;
phi=74;


% Initial Conditions

Pfstart(1:n)=0.0; Jfstart(1:n)=0.0; Sfstart(1:n)=0.0; Ifstart(1:n)=0.0;
Jmstart(1:n)=0.0; Smstart(1:n)=0.0; Imstart(1:n)=0.0;
Nfstart(1:n)=0.0; Nmstart(1:n)=0.0;
lambdaf=1; lambdam=1;

% Initial Conditions

Nfstart=exp(-(0.0000189*exp(0.1*(a))));
Nmstart=exp(-(0.0000354*exp(0.098*(a))));
L=da; l=7/64;
Pfstart=Nfstart.*(1-0.9./(1+exp(16.3-a))).*p.*...
...(cos((pi*((a-12)./74-L))/(2*l))).^3; j1=ceil((L+l)/da); Pfstart(j1:n)=0;
Jfstart=((1-0.9./(1+exp(16.3-a))).*Nfstart-Pfstart);
Ifstart=(0.23.*exp(-((a-21.8)./12.5).^2)).*(0.9./(1+exp(16.3-a))).*Nfstart;
Sfstart=(1-0.23.*exp(-((a-21.8)./12.5).^2)).*...
...(0.9./(1+exp(16.3-a))).*Nfstart;
Smstart=(1-0.23.*exp(-((a-21.8)./12.5).^2)).*...
...(0.9./(1+exp(13.3-0.8*a))).*Nmstart;
Jmstart=(1-0.9./(1+exp(13.3-0.8*a))).*Nmstart;
Imstart=(0.23.*exp(-((a-21.8)./12.5).^2)).*...
...(0.9./(1+exp(13.3-0.8*a))).*Nmstart;

Pfeno4=Pfstart; Jfeno4=Jfstart; Sfeno4=Sfstart; Ifeno4=Ifstart;
```

```
Jmeno4=Jmstart; Smeno4=Smstart; Imeno4=Imstart;
Nfeno4=Nfstart; Nmeno4=Nmstart;

% Parameter values

beta=0.6; gammaf=0.8; gammam=0.8;

for j=1:N2;

    Pfeno4star=enoadvection(Pfeno4,n,da,dt,2);
    Jfeno4star=enoadvection(Jfeno4,n,da,dt,2);
    Sfeno4star=enoadvection(Sfeno4,n,da,dt,2);
    Ifeno4star=enoadvection(Ifeno4,n,da,dt,2);
    Jmeno4star=enoadvection(Jmeno4,n,da,dt,2);
    Smeno4star=enoadvection(Smeno4,n,da,dt,2);
    Imeno4star=enoadvection(Imeno4,n,da,dt,2);
    Nfeno4star=enoadvection(Nfeno4,n,da,dt,2);
    Nmeno4star=enoadvection(Nmeno4,n,da,dt,2);

    for i=2:n-1
        k=(i).*da.*74;
        if  k <= 7
            etaf=((exp((-((k+12)-16.95)^2)/(2*(1.33^2))))/(1.33*sqrt(2*pi)));
            etam=((exp(-((k+12)-16.58)^2/(2*(1.14^2))))/(1.14*sqrt(2*pi)));
          else
            etaf=0.06; etam=0.06;
        end

       if k < 4
              zm=0.1411*(k+12);
              zf=0.1411*(k+12);
        elseif k >= 4 && k <= 57;
            zm=2.93-0.042*(k+12);
            zf=2.93-0.042*(k+12);
            else
            zm=0;
            zf=0;
```

```
    end
    alpha=0.003*(k+12);

% Contact Matrix A
    A=zeros(n,n);
    for ii=1:n;
        for jj=1:n;
            if jj==ii;
                A(ii,jj)=0.5;
            elseif jj==ii+1;
                A(ii,jj)=0.125;
            elseif jj==ii-1;
                A(ii,jj)=0.125;
            elseif jj==ii+2;
                A(ii,jj)=0.125;
            elseif jj==ii-2;
                A(ii,jj)=0.125;
            end
        end
    end
    A(1,2)=0.25; A(1,3)=0.25; A(2,1)=0.25;
    A(n-1,n)=0.25; A(n,n-2)=0.25; A(n,n-1)=0.25;

    % Integral part of lambda

    lambdaf(i)=sum(A(i,:).*(Imeno4)./(Nmeno4-Jmeno4));
    lambdam(i)=sum(A(i,:).*(Ifeno4)./(Nfeno4-Jfeno4));

% Solving the equations

    Pfneweno4(i)=Pfeno4star(i)
    +74.*( -dt.*(alpha+1.*0.0000189*exp(0.1*(k+12)))*Pfeno4(i) );
    Jfneweno4(i)=Jfeno4star(i)
    +74.*( +dt.*(-(etaf+1.*0.0000189*exp(0.1*(k+12)))*Jfeno4(i)+...
    ...(0.616*alpha+0.05)/(1+alpha)*alpha*Pfeno4(i)) );
    Sfneweno4(i)=Sfeno4star(i)+
    74.*( +dt.*((1-(0.616*alpha+0.05)/(1+alpha))*alpha*Pfeno4(i)+...
```

```
    ...etaf*Jfeno4(i)-(zf*beta*lambdaf(i)+...
    ...1.*0.0000189*exp(0.1*(k+12)))*Sfeno4(i)+gammaf*Ifeno4(i)) );
    Ifneweno4(i)=Ifeno4star(i)
    +74.*( +dt.*(zf*beta*Sfeno4(i)*lambdaf(i)-...
    ...(gammaf+1.*0.0000189*exp(0.1*(k+12)))*Ifeno4(i)) );
    Jmneweno4(i)=Jmeno4star(i)
    +74.*( -dt.*((etam+(1.*0.0000347*exp(0.098*(k+12))))*Jmeno4(i)) );
    Smneweno4(i)=Smeno4star(i)
    +74.*( +dt.*(etam*Jmeno4(i)-(zm*beta*lambdam(i)+...
    ...(1.*0.0000347*exp(0.098*(k+12))))*Smeno4(i)+gammam*Imeno4(i)) );
    Imneweno4(i)=Imeno4star(i)
    +74.*( +dt.*(zm*beta*Smeno4(i)*lambdam(i)-...
    ...(gammam+(1.*0.0000347*exp(0.098*(k+12))))*Imeno4(i)) );
    Nfneweno4(i)=Nfeno4star(i)
    +74.*( -dt.*(1.*0.0000189*exp(0.1*(k+12)))*Nfeno4(i) );
    Nmneweno4(i)=Nmeno4star(i)
    +74.*( -dt.*(1.*0.0000347*exp(0.098*(k+12)))*Nmeno4(i) );


end

% Boundary Conditions

Nfneweno4(1)=1;
Nfneweno4(n)=Nfneweno4(n-1);
Nmneweno4(1)=1;
Nmneweno4(n)=Nmneweno4(n-1);
Pfneweno4(1)=p.*(1-0.9./(1+exp(16.3-12))).*Nfneweno4(1);
Pfneweno4(n)=Pfneweno4(n-1);
Ifneweno4(1)=(0.23.*exp(-((12-21.8)./12.5).^2)).*...
...(0.9./(1+exp(16.3-12))).*Nfneweno4(1);
Ifneweno4(n)=Ifneweno4(n-1);
Sfneweno4(1)=(1-0.23.*exp(-((12-21.8)./12.5).^2)).*...
...(0.9./(1+exp(16.3-12))).*Nfneweno4(1);
Sfneweno4(n)=Sfneweno4(n-1);
Jfneweno4(1)=((1-0.9./(1+exp(16.3-12))).*Nfneweno4(1)-Pfneweno4(1));
Jfneweno4(n)=Jfneweno4(n-1);
```

```
    Imneweno4(1)=(0.23.*exp(-((12-21.8)./12.5).^2)).*...
    ...(0.9./(1+exp(13.3-0.8*12))).*Nmneweno4(1);
    Imneweno4(n)=Imneweno4(n-1);
    Smneweno4(1)=(1-0.23.*exp(-((12-21.8)./12.5).^2)).*...
    ...(0.9./(1+exp(13.3-0.8*12))).*Nmneweno4(1);
    Smneweno4(n)=Smneweno4(n-1);
    Jmneweno4(1)=(1-0.9./(1+exp(13.3-0.8*12))).*Nmneweno4(1);
    Jmneweno4(n)=Jmneweno4(n-1);


    Pfeno4=Pfneweno4; Jfeno4=Jfneweno4; Sfeno4=Sfneweno4;
    Ifeno4=Ifneweno4;
    Jmeno4=Jmneweno4; Smeno4=Smneweno4; Imeno4=Imneweno4;
    Nfeno4=Nfneweno4; Nmeno4=Nmneweno4;

% Class sizes over time

    Pfsum(j)=sum(Pfeno4); Jfsum(j)=sum(Jfeno4); Sfsum(j)=sum(Sfeno4);
    Ifsum(j)=sum(Ifeno4);
    Jmsum(j)=sum(Jmeno4); Smsum(j)=sum(Smeno4); Imsum(j)=sum(Imeno4);
    Nfsum(j)=sum(Nfeno4); Nmsum(j)=sum(Nmeno4);

end

% Plot the classes after final time;
the difference between the classes initially and after final time;
the class sizes over time and the initial conditions.

figure(1)
set(gca,'FontSize',14)
set(legend,'FontSize',14)
plot(a,Pfeno4,'LineWidth',3)
hold on
plot(a,Jfeno4,'--k','LineWidth',3)
hold on
plot(a,Sfeno4,'-.k','LineWidth',3)
hold on
```

```
plot(a,Ifeno4,':k','LineWidth',3)
hold on
plot(a,Nfeno4,'k','LineWidth',3)
hold on
plot(a,Jmeno4,'--', 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
plot(a,Smeno4,'-.', 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
plot(a,Imeno4,':', 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
plot(a,Nmeno4, 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
legend('P_F', 'J_F', 'S_F', 'I_F', 'N_F', 'J_M', 'S_M', 'I_M', 'N_M')
xlabel('age')
ylabel('Population')

disp(74.*dt.*N2)

figure(2)
set(gca,'FontSize',14)
set(legend,'FontSize',14)
plot(74.*dt.*(1:N2),Pfsum,'LineWidth',3)
hold on
plot(74.*dt.*(1:N2),Jfsum,'--k','LineWidth',3)
hold on
plot(74.*dt.*(1:N2),Sfsum,'-.k','LineWidth',3)
hold on
plot(74.*dt.*(1:N2),Ifsum,':k','LineWidth',3)
hold on
plot(74.*dt.*(1:N2),Nfsum,'k','LineWidth',3)
hold on
plot(74.*dt.*(1:N2),Jmsum,'--', 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
plot(74.*dt.*(1:N2),Smsum,'-.', 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
plot(74.*dt.*(1:N2),Imsum,':', 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
```

```
plot(74.*dt.*(1:N2),Nmsum,'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
legend('P_F', 'J_F', 'S_F', 'I_F', 'N_F', 'J_M', 'S_M', 'I_M', 'N_M')
xlabel('time')
ylabel('Population')

figure(3)
set(gca,'FontSize',14)
set(legend,'FontSize',14)
plot(a,Pfstart,'LineWidth',3)
hold on
plot(a,Jfstart,'--k','LineWidth',3)
hold on
plot(a,Sfstart,'-.k','LineWidth',3)
hold on
plot(a,Ifstart,':k','LineWidth',3)
hold on
plot(a,Nfstart,'k','LineWidth',3)
hold on
plot(a,Jmstart,'--', 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
plot(a,Smstart,'-.', 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
plot(a,Imstart,':', 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
plot(a,Nmstart, 'Color',[0.8, 0.8, 0.8],'LineWidth',3)
hold on
legend('P_F', 'J_F', 'S_F', 'I_F', 'N_F', 'J_M', 'S_M', 'I_M', 'N_M')
xlabel('age')
ylabel('Population')

%sum(Jfstart)

figure; plot((a),Pfstart,'k',(a),Pfeno4,'b')
figure; plot((a),Jfstart,'k',(a),Jfeno4,'r')
figure; plot((a),Sfstart,'k',(a),Sfeno4,'b')
figure; plot((a),Ifstart,'k',(a),Ifeno4,'r')
```

```
figure; plot((a),Jmstart,'k',(a),Jmeno4,'b')
figure; plot((a),Smstart,'k',(a),Smeno4,'r')
figure; plot((a),Imstart,'k',(a),Imeno4,'b')
figure; plot((a),Nfstart,'k',(a),Nfeno4,'r')
figure; plot((a),Nmstart,'k',(a),Nmeno4,'b')
```

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